A paradigm shift in the CBW proliferation problem: devising effective restraint on the evolving biochemical threat

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A Paradigm Shift in the CBW Proliferation Problem: Devising Effective Restraint on the Evolving Biochemical Threat[1]

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Executive Summary

Characteristic of the developments in science and technology over the past three decades is the explosive nature of the accumulation of knowledge concerning the mechanisms and functions of biological systems. In this regard, the associations between science and technology and political decision-making processes within the context of arms control negotiations were at the centre of this investigation. In the light of the collapse of negotiations in Geneva over a verification protocol to the Biological and Toxins Weapons Convention (BWC), a new assessment of these associations is all the more urgent.

A scientifically based analysis of the possibilities for misuse of developments for the production of biological weapons was carried out in order to make particular risk areas for arms control and verification of biological weapons more visible. Clear evidence was obtained for a paradigm shift in the CBW proliferation problem with its focus moving away from the malign manipulation of microorganisms to cause infectious diseases to the possibility of using biochemical agents as weapons to specifically target the operation of interacting biological systems in the human body. Two vital, interacting systems - the neuroendocrine and the immune systems with their double vulnerability to modulation-were analysed in this context. The analysis of these two systems regarding in the life sciences illustrates that much of the growing knowledge is dual-use and could be subject to hostile misuse if the prohibitionary norm embodied in the BWC is not upheld in coming decades. Although the controls of science and technology that are increasingly taking shape in the United States point in the right direction, they face the same shortcomings as do the deliberations by states parties to the BWC in the so-called new process created by the last BWC Review Conference: both of these attempts do not lead to coordinated action on the international level and are thus decoupled from developing the regime as a whole.

The prohibitionary norm of the Chemical Weapons Convention (CWC) is also under threat by developments in science and technology. Indeed, many of the products flowing from the revolutions in biotechnology and pharmacology that can impact life processes at various levels are basically chemical compounds that have relevance for both the BWC and the CWC. Negotiators of the CWC have provided for a procedure to review developments in science and technology by creating the Scientific Advisory Board (SAB) to advise the Organization for the Prohibition of Chemical Weapons (OPCW) on science and technology matters. This body has expressed its concerns about the development of riot control agents and other so-called “non-lethal” chemical weapons. However, S&T issues did not have a prominent position on the agenda of the First Review Conference of the CWC. In order to prevent the misuse of twenty-first century chemistry, CWC implementation cannot continue as if the regime existed in a time warp. Otherwise, science and technology advances in chemistry, biology and the life sciences in general can be expected to again leave their mark on military thinking and the history of warfare.

Finally, the results of these analyses were used to examine how to devise an overarching framework that would tie together all the measures that have been proposed and that will be needed additionally to counter biochemical warfare.

Zusammenfassung

In den vergangenen drei Jahrzehnten ist das akkumulierte Wissen über die Mechanismen und Funktionen biologischer Systeme durch wissenschaftliche und technologische Entwicklungen explosionsartig gewachsen. Der vorliegende Forschungsbericht untersucht die Wechselwirkung von naturwissenschaftlicher Forschung, insbesondere in der Biotechnologie und Molekularbiologie, und politischem Steuerungshandeln im Bereich der Rüstungskontrolle. Vor dem Hintergrund der gegenwärtigen Krise der Genfer Verhandlungen über ein Verifikationsprotokoll zum „Übereinkommen über das Verbot der Entwicklung, Herstellung und Lagerung bakteriologischer (biologischer) Waffen und Toxinwaffen“ (BWÜ) ist es dringend erforderlich, den Handlungsbedarf für die Rüstungskontrollpolitik neu zu bestimmen.

Die Verfasser untersuchten die Missbrauchsmöglichkeiten neuer Forschungserkenntnisse und Technologieentwicklungen für die Herstellung von Biowaffen auf der Grundlage einer naturwissenschaftlichen Analyse. In der Studie konnten besondere „Risikobereiche“ identifiziert und sichtbar gemacht werden, die für die Rüstungskontrollpolitik und für Verifikationssysteme zu biologischen Waffen von grundlegender Bedeutung sind. Hierbei traten deutliche Hinweise auf einen Paradigmenwechsel bei den Proliferationsgefahren für biologische und chemische Waffen zutage: Lag die Hauptgefahr bisher im Einsatz modifizierter Mikroorganismen, um Infektionskrankheiten auszulösen, so steht nun die Möglichkeit im Vordergrund, biochemische Agenzien als Waffen zu benutzen, um gezielt die Funktionsweise und Interaktion biologischer Systeme im menschlichen Körper anzugreifen. Im Zentrum der Untersuchung standen zwei lebenswichtige, miteinander verbundene physiologische Systeme - das Nerven- und das Immunsystem, die eine doppelte Verletzbarkeit durch Manipulationen aufweisen und somit eine grundsätzliche Relevanz für die biochemische Rüstungskontrolle besitzen. Eine Analyse dieser Systeme im Kontext jüngster Entwicklungen in den Lebenswissenschaften (Life Sciences) verdeutlicht, dass ein Großteil des gestiegenen Wissens einen *dual-use*-Charakter hat und somit für nicht-friedliche Zwecke missbraucht werden kann, sofern die Verbotsnormen des BWÜ in dem kommenden Jahrzehnten nicht angepasst werden. Die Kontrollen von Wissenschaft und Technologieentwicklung, wie sie in letzter Zeit in vermehrtem Ausmaß in den Vereinigten Staaten eingerichtet wurden, weisen zwar in die richtige Richtung. Sie sind jedoch mit denselben Unzulänglichkeiten behaftet, die auch die Konferenzen der BWÜ-Vertragsstaaten kennzeichnen. Auch die Maßnahmen im Rahmen des so genannten „neuen Prozesses“, der auf der letzten Überprüfungskonferenz des BWÜ initiiert wurde, führten nicht zu koordinierten Vorgehensweisen auf der internationalen Ebene und sind somit nicht in die Regimeentwicklung integriert.

Die Verbotsnormen des Chemiewaffenübereinkommens (CWÜ) geraten durch die dynamische Entwicklung von Forschung und Technologie ebenfalls in Gefahr. Zahlreiche Produkte, die aus der neueren Biotechnologie und Pharmakologie hervorgegangen sind, können Lebensprozesse auf den verschiedensten Ebenen beeinflussen. Sie bestehen im Wesentlichen aus chemischen Verbindungen, die sowohl für das BWÜ als auch für das CWÜ von Relevanz sind. Die Verhandlungsführer des CWÜ sprachen sich für die Gründung eines wissenschaftlichen Beratungsgremiums (*Scientific Advisory Board*) aus, um Entwicklungen in Forschung und Technologie überprüfen zu können und die Überwachungsorganisation für das Verbot chemischer Waffen (OPWC) in Den Haag in diesen Fragen zu beraten. Dieses Gremium äußerte seine Bedenken über die Entwicklung von so genannten *riot control agents* und anderen „nichttödlichen“ chemischen

Waffensystemen. Trotzdem spielten Fragen der Forschung und Technologieentwicklung auf der Ersten Überprüfungskonferenz des CWÜ keine bedeutende Rolle. Wenn der Missbrauch der modernen Chemie im 21. Jahrhundert verhindert werden soll, darf die Umsetzung des CWÜ nicht in einer Weise fortgesetzt werden, als ob die wissenschaftliche und technologische Basis unverändert bliebe. Andernfalls ist zu befürchten, dass die wissenschaftlichen und technologischen Entwicklungen in der Chemie und Biologie sowie in den Lebenswissenschaften im Allgemeinen erneut ihre Spuren im militärischen Denken und in der Geschichte der Kriegsführung hinterlassen werden.
Die Ergebnisse der Forschungsarbeiten dienten dazu, einen übergreifenden Rahmen zu entwerfen, der die bereits vorhandenen Vorschläge mit den zusätzlich erforderlichen Maßnahmen zusammenführt, um einer künftigen biochemischen Kriegsführung entgegenzuwirken.

1 Introduction

The norm against the deliberate use of poison and disease in warfare can be traced back several hundred if not thousand years. This 'taboo' became embodied in the 20th Century in three international treaties which form the basis of the two chemical and biological weapons prohibition regimes that are still today the major instruments in the fight against the spread of biological and chemical weapons proliferation and use. The three legal instruments are the 1925 Geneva Protocol, the 1972 Biological and Toxin Weapons Convention (BWC) and the 1993 Chemical Weapons Convention (CWC).

The 1925 Geneva Protocol came about as a reaction against the misuse of modern chemistry in the form of 'gas' warfare during World War I. It prohibits the use of chemical and biological - or, as in the terminology of the day, 'bacteriological' - weapons in warfare. Not prohibited are for example development and stockpiling of chemical or biological warfare agents. In addition, many states parties to the 1925 Geneva Protocol attached unilateral reservations to their ratifications, which limited the scope of the Protocol even further. During the second half of the 1960s negotiations to comprehensively prohibit chemical and biological weapons (CBW) were separated, which in turn led to the conclusion of the 1972 BWC. While the BWC was hailed as the first multilateral agreement to ban a whole class of weapons of mass destruction, the 1993 CWC has to be regarded as one of the most advanced instruments of multilateral arms control. The CWC not only bans a category of weapons of mass destruction, but is the first such multilateral treaty that sets up a new international organisation for the verification of treaty provisions.

It has become clear over the last few years, however, that the adequacy of the two prohibition regimes which aim at preventing the hostile use of chemistry and biology for offensive military or for terrorist purposes has been seriously called into question. This is due to a series of interrelated events and trends:

- The nerve gas attack in the Tokyo subway system in March 1995 by the apocalyptical sect *Aum Shinrikyo* has often been called a 'wake-up call,' refocusing attention as to the potential sources of a CBW attack.[2] In addition, the anthrax letters sent through the US mail system in 2001 seemed to confirm that terrorists can use biological weapons.
- With respect to the BWC, however, the most glaring gap in the controls of this treaty is the absence of a verification system that would be able to confirm the treaty compliant behaviour of BWC states parties or uncover violations of the treaty. Also, the parallel process of strengthening the BWC through a legally binding international instrument (protocol to the BWC) that was started in 1991 came to an abrupt - and unsuccessful - end in July 2001.[3]
- The chemical weapons prohibition regime is much farther developed than its BW counterpart. Yet, a number of problems have come to the fore, the two most important of which relate first, to the implementation of several CWC provisions and second, to the unwillingness in part of a number of CWC states parties to keep the regime up to

2 See D. E. Kaplan and A. Marshall, The Cult at the End of the World. London: Hutchinson, 1996; M. Leitenberg, The Experience of the Japanese Aum Shinrikyo Group and Biological Agents, In: B. Roberts (ed.), Hype or Reality: The "New Terrorism" and Mass Casualty Attacks. Alexandria, VA: CBACI, 2000, pp.159-170.

3 Dando, M.R.: Preventing Biological Warfare. The Failure of American Leadership Basingstoke: Palgrave Macmillan 2002.

date with a view to adapting verification provisions to the changing face of the chemical industries worldwide.

- The issue of so-called ‘non-lethal’ or ‘less than lethal’ chemical weapons. During recent years there seems to have been an increase in interest in toxic incapacitants in the US, Russia and other countries.
- Lastly, a series of scientific experiments and their subsequent publication suggests that the range and possibilities for malign use of biology and chemistry have greatly increased.[4]

While these experiments of concern mostly represent another variation of the theme of modifying or “improving” disease-causing agents, there is different, more fundamental change under way in the life sciences. This paradigm shift is fuelled by the decoding of the human genome and finds its expression in the establishment of new scientific subfields such as systems biology. This means that the current scientific and technological revolution in the life sciences changes the focus of the proliferation problem from the chemical or biological warfare agent as the object of malign manipulation to the physiological target in the human body as the object of attack. The revolution in the life sciences cannot but raise the question of the implications this change in our understanding of the human body at the molecular level will have for the normative structure of the two prohibition regimes currently in place.

In general terms the CBW threat is best conceived of as a chemical and biological spectrum ranging from classical lethal chemical warfare agents on one end to toxic industrial chemicals and on to mid-spectrum toxins and bioregulators. On the other end it ranges from traditional to genetically modified biological warfare agents on through to newly designed agents. It is to be expected that the scope and pace of scientific and technological change in the life sciences will affect all aspects of this spectrum.

The two prohibition regimes in their current shape are ill equipped to prevent the misuse of scientific and technological advances across the spectrum of the revolution in the life sciences. The goal, then, has to be to adapt the CW and BW prohibition regimes so that they provide an adequate framework for state action and interaction to address the challenges ahead. In this context we understand regime adequacy to be composed of regime effectiveness and regime robustness, two concepts which are interrelated, but not identical. Regime effectiveness on one hand falls broadly within the scholarly debates on international regimes.[5] In these debates there is consensus that the effectiveness of an international regime has two dimensions: first it focuses on the question whether regimes affect state behaviour in the issue area they are set up to regulate. Secondly, regime effectiveness is measured by the impact the regime has on observable data in the issue area. In our area of concern the two aspects of regime effectiveness are closely related: if states do neither acquire nor use chemical or biological weapons then the goal of prohibiting these weapons has also been achieved - at least if the regime enjoys a universal membership.

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4 Jackson, R. J./Ramsay, A. J./Christensen, C./Beaton, S./Hall, D. F. R./Ramshaw, I. A.: Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. In: Journal of Virology 75 (2001), pp. 1205-1210; Cello, J./Paul, A.V./Wimmer, E.: Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. In: Science 297 (2002), pp. 1016-1018.

5 Levy, M.A. et al.: The study of international regimes. In: European Journal of International Relations 1 (1995), pp. 267-330; Hasenclever, A./Mayer, P./Rittberger, V.: Theories of International Regimes. Cambridge: Cambridge University Press (1997).

On the other hand, a regime displays robustness when the actors' expectations continue to converge around the regime's normative structure, despite the occurrence of stress factors that challenge the regime. [6] Müller et.al.[7] identify a number of stress factors that can undermine a regime's robustness, two of which are of particular importance for our purposes: technological change and shifts in the distribution of power. Many security regimes exist in issue areas which are influenced heavily by technological change. On the one hand, technological developments can create new problems which are no longer adequately covered by regime rules and procedures. On the other hand, such developments might offer new tools for problem-solving, thereby creating the impression that existing instruments have become obsolete. Regardless of its direction, technological change, if left unattended over longer periods of time, can undermine regime robustness and thus necessitate the formulation of new regime norms and rules. The likelihood that such adaptations are made is influenced to a considerable degree by the distribution of power among regime members. Shifts in power distribution can have their origins outside the regime and well be able to transgress the regimes scope. Or such shifts can be caused by technological breakthroughs in the issue area a regime regulates, which benefits only one or a small group of states participating in the regime.

Our central concern then is with scientific and technological advances in the life sciences that can be expected to undermine the adequacy of the CW and BW prohibition regimes, if these advances are left unattended. In order to address this concern we raise four questions:

1. How are the CW and BW prohibition regimes set up to deal with scientific and technological (S&T) changes affecting the issue areas these regimes are to regulate?
2. What are the areas of concern in terms of S&T advances that might undermine the two regimes' adequacy?
3. How well equipped are the two regimes to deal with the new challenges?
4. Which adaptations of the CW and BW prohibition regimes are needed to bring them into line with the realities of 21st century life sciences?

The following chapters will address these questions.

6 Hasenclever, A./Mayer, P./Rittberger, V.: Fair Burden-Sharing and the Robustness of International Regimes: The Case of Food Aid. Tübinger Arbeitspapiere zur Internationalen Politik und Friedensforschung Nr.31. Tübingen (1998), p.1.

7 Müller, H. et al.: Regime unter Stress. Beharrungs- und Anpassungsleistungen internationaler Regime unter den Bedingungen existenzgefährdender Herausforderungen. Frankfurt/Main: PRIF, February 1999, pp. 10-11, 15-24, unpublished manuscript.

2 Science, Technology and the CBW Regimes

Advances in science and technology (S&T) can have both positive and negative effects on societies and the relations among them. In chemistry, biology and the life sciences more generally the intention of scientists doing cutting-edge research will generally be to better the human condition, such as through the development of new medicines. However, a considerable number of chemical compounds and micro organisms have potential for harmful, as well as beneficial, effects.

Many toxic chemicals, their precursors, as well as pathogens and processes involved in their production have perfectly legitimate civilian applications. At the same time the history of chemistry and biology provides ample examples of new discoveries in these areas being used for weapons' purposes. Thus, the dual-use character of toxic chemicals and pathogenic micro organisms is not just an abstract quality they possess. Rather, the different purposes to which these substances and organisms can be put have had profound implications on military thinking and - in the case of chemical weapons (CW) - the history of warfare. Any effort to control the use of toxic chemicals or pathogenic micro organisms for offensive military purposes has to take into account the dual-use nature of many of these chemicals, organisms and related equipment and processes.

The next section will present a discussion of present control mechanisms for chemical and biological weapons (CBW) and how they relate to the state of development of the life sciences. The final section will analyse how the biotechnology revolution might impact the future of CBW controls. Given the availability of detailed analyses of some aspects of the biotechnology revolution and its impact on BW controls, in general this paper will focus more on the impact on CW controls.

2.1 Present CBW Control Mechanisms and Their Relationship to Developments in the Life Sciences[8]

The CBW control regimes go back to the 1925 "Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous, or Other Gases, and of Bacteriological Methods of Warfare". The Protocol was originally conceived as a response to the widespread use of CW during the First World War, and only upon a Polish initiative were 'bacteriological methods of warfare' included into the Protocol text. It entered into force in 1928 and has currently 133 member states. Today, the CBW regimes revolve around two international treaties: the Biological and Toxin Weapons Convention (BWC)[9] and the Chemical Weapons Convention (CWC).[10]

The CWC was opened for signature in January 1993 and entered into force on 29 April 1997. It bans the development, production, use and retention of CW and requires states

8 Kelle, A./Nixdorff, K./Dando, M.: Controlling Biochemical Weapons. Adapting Multilateral Arms Control for the 21st Century, Basingstoke: Palgrave Macmillan 2006, 208 pp.; Aftalion, F.: A History of the International Chemical Industry. From the "Early Days" to 2000 (2nd ed.). Philadelphia: Chemical Heritage Press, (2001), especially pp. 32-101; Robinson, J.P.:1998, The Negotiations on the Chemical Weapons Convention: a historical overview. In: Bothe,M./Ronzitti, N./Rosas, A. (eds.): The New Chemical Weapons Convention-Implementation and Prospects. The Hague: Kluwer Law International (1998), pp. 17-36.

9 Also known as the BTWC. See <http://www.opbw.org> for the convention's text and most review conference documents issued over the thirty-year history of the BWC.

10 See <http://www.opcw.org> for the CWC's text and other useful related information.

possessing CW to destroy them over a ten-year period. The dual-use problem led to the inclusion in the CWC of the so-called general purpose criterion. According to this provision, toxic chemicals that could be misused as CW are not prohibited altogether. Negotiators of the CWC also realized that the area the convention regulates would be subject to advances in S&T. They have therefore provided for a procedure to review these developments at CWC review conferences and created the Scientific Advisory Board (SAB) to advise the Organisation for the Prohibition of Chemical Weapons (OPCW) on S&T matters.

Chemical warfare agents and means for their production are based on long-established, well-known and proven technologies. Thus, a potential proliferator does not necessarily have to look for the latest developments in chemistry or related disciplines to obtain a militarily significant CW capability. Nevertheless, at least three developments are taking place in both the civilian and military applications of chemistry that might well change the way we (need to) think about chemical warfare agents and the ways and means to prevent the misuse of toxic chemicals for offensive military purposes. Two of these developments - the evolution of chemical industry, and the renewed interest in “non-lethal” weapons - are directly linked to the CW control regime and its effectiveness. The third one, the impact of the biotechnology revolution on the long-term viability or robustness of the CW control regime, will be discussed in the final section.

2.1.1 Evolution of the Chemical Industry

Two developments in the chemical industry pose particular challenges to the verification of the peaceful applications of toxic chemicals. First, there is a clear trend away from the continuous production of large quantities of a chemical in a facility specifically designed for the purpose. Rather, many companies increasingly rely on the use of smaller, more versatile production facilities, which can be adapted from the production of a batch of one chemical to another one in a short period of time. Such facilities could easily fall through the cracks of the declaration and inspection system of the CWC. Utilization of such batch-production facilities would theoretically enable a potential proliferator to distribute the production of CW precursor chemicals or even chemical warfare agents themselves among a number of such facilities to avoid detection.

Secondly, over the last decade a considerable number of traditional chemical firms were broken up and replaced by so-called “industrial parks”. This poses a potential problem for verification under the CWC as the convention’s definitions that form the basis for the verification measures assume the existence of plant sites - which were prevalent in the late 1980s when the CWC was negotiated. Verification procedures have to be adapted to the changed environment. However, many CWC states parties are not inclined to support such an adaptation. Instead they argue that the OPCW’s industry verification activities should remain unchanged, thereby risking that the regime will become irrelevant due to developments in chemical industry at some point in the future.[11]

11 Kelle, A.: The CWC after its first review conference: is the glass half full or half empty? In: Disarmament Diplomacy 71 (2003), pp. 31-40.

2.1.2 Interest in “Non-lethal” Weapons

Equally important, renewed interest in so-called “non-lethal” CW threatens to undermine the current control regime and calls into question its future robustness. If there was the need for a wake-up call to raise awareness of this problem, this was most certainly provided by the use of a “fentanyl-derivative” - as it was called by Russian authorities - to end the Moscow theatre hostage crisis in 2002.[12] However, this incident represents just the tip of the iceberg, as Russia is not the only state interested in utilizing “non-lethal” CW in a number of police and military scenarios other than war. Certainly the US military shows a strong interest in developing this kind of capability.[13]

From a scientific and technical point of view the major problem with “non-lethal” weapons lies in the fact that they are not non-lethal, as the Moscow theatre situation has clearly demonstrated: about 130 of the 830 hostages died from the effects of the gas used. This represents a mortality rate of approximately 16%. In comparison, the chemical warfare agents of the First World War like chlorine, phosgene and mustard gas, which are prohibited under the CWC and listed on its schedules of chemicals, have a lethality of around 7%. [14]

Even if truly non-lethal CW were technically feasible, is it questionable whether their use would have the effect to merely incapacitate temporarily and not lead to the death of those exposed to the agents. Again, the Moscow theatre scenario offers some insights: Russian security forces obviously had orders to shoot the hostage-takers, which were incapacitated by the gas used in the theatre. Although this might have been the best way to ensure that none of the hostage-takers would be able to detonate their explosives, it reveals a central weakness of the argument of proponents of “non-lethal” CW. These incapacitants are often used in conjunction with lethal military force and in this context act mainly as a force multiplier and not as a life-saving tool. Exactly the same pattern of “non-lethal” CW usage occurred during the Viet Nam War, in which the US military employed 10 million pounds of the irritant CS.[15]

Before the First CWC Review Conference a number of contributions on S&T developments of relevance to the CWC were made by NGOs, including the International Union of Pure and Applied Chemistry, which were then taken up by organs of the OPCW, states parties individually and most notably the SAB. [16] S&T issues did not, however, have a prominent position on the agenda of the Review Conference. Nevertheless, S&T issues-more specifically the Report of the SAB as submitted to the conference by the Director-General - resurfaced in the Review Document, both in the sections on general verification provisions and on activities not prohibited under the CWC.

Although the topics of “non-lethal” weapons and chemical incapacitants received considerable attention in the run-up to the meeting, discussion on them was almost completely suppressed during the Conference. The only opportunity to discuss these matters publicly arose at the “Open Forum on the Chemical Weapons Convention”, hosted by the OPCW and supported by a number of NGOs. The Open Forum included a panel discussion entitled “The Chemical Weapons Ban and the Use of Incapacitants in Warfare

12 Wax, P.E./Becker, C.E./Curry, S.C.: Unexpected “gas” casualties in Moscow: a medical toxicology perspective. In: Annals of Emergency Medicine 41 (2003), pp. 700-705.

13 See the website of the Sunshine Project for documentation of the US non-lethal weapons programmes, at <www.sunshine-project.org>.

14 SIPRI: The Problem of Chemical and Biological Warfare. Volume I: The Rise of CB Weapons. Stockholm: Almqvist and Wiksell 1971, pp. 26-58.

15 CBW. “Non-Lethal” weapons, the CWC and the BWC, Editorial. In: The CBW Conventions Bulletin no. 61 (2003), p. 2.

16 OPCW, Note by the Director-General. Report of the Scientific Advisory Board on Developments in Science and Technology, document RC-1/DG.2. The Hague: United Nations, 23 April 2003, p. 15.

and Law Enforcement". Not surprisingly, then, the text of the Review Document did not contain any language explicitly referring to incapacitants or "non-lethal" weapons. However, the document did contain language in relation to the definitions in Article II of the Convention, pointing out that these were found by the conference to adequately cover developments in science and technology.

Turning to biological weapons, the BWC stipulates in its Article I that:

> "Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:
> (1) Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes". [17]

Like in the case of the CWC, the general purpose criterion not only makes it clear that peaceful uses of the biosciences are legitimate undertakings for states parties to the BWC, but also allows the use of pathogenic organisms or toxins in quantities and for purposes other than use as weapons. However, unlike the CW control regime, there are neither verification provisions foreseen in the BWC nor has an international organization been set up to oversee the implementation of the regime provisions. States parties are left to address S&T advances at the BWC review conferences and include their assessment as to relevant S&T developments and their impact on the BW control regime in the final documents issued by these conferences. Up to the Fifth Review Conference (2001-2002), successive review conferences have found the possible misuse of S&T advances in the life sciences to be covered by the scope of the BWC.

Unfortunately, due to the failure to negotiate a Final Document during the Fifth Review Conference, the interpretations by BWC states parties concerning scientific advances of relevance to the BWC since the Fourth Review Conference (for over ten years) have not been recorded in a consensual document.

2.2 The Biotechnology Revolution and the Future of CBW Controls

It is commonly assumed that the biotechnology revolution and the increased utilization of genetic engineering will only impact the BW control regime, and not (or only marginally) the CW control regime. Yet what is often overlooked is the fact that many of the products flowing from the biotechnology revolution that can impact life processes at various levels are basically chemical compounds. All chemical compounds that have toxic properties fall under the prohibitions of the CWC. More specifically, the dangers stemming from an uncontrolled twenty-first century chemistry are twofold: first, new toxic biochemical compounds, which are highly effective at low dosage levels, could be developed and used as CW. This would undermine the prohibitory norm against CW. The second danger lies in the possible circumvention strategies for the production of known - or novel - CW agents, which these new technologies might offer to a determined proliferator. Developments with respect to both of these areas are likely to challenge our current understanding of what is a chemical weapon.

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17 United Nations: Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. United Nations General Assembly Resolution 2826 (XXVI), United Nations, New York 1972. Full text available at <http://www.opbw.org>.

The chemistry of the twenty-first century is a far cry from the one of the 1980s, which guided negotiations for the CWC verification regime. Chemistry now utilizes other scientific disciplines and technologies in its quest for new chemical compounds. Especially in the area of drug development and delivery, scientific and technological advances in biotechnology and genomics, robotics,[18] information technology[19] and nanotechnology[20] act as enablers of combinatorial chemistry and high throughput screening, which in turn have become the driving forces in pharmaceutical research and development.[21]

The genomics revolution, in particular progress in functional genomics (the ability to attribute specific functions to a particular gene), furthers our understanding of fundamental life processes at a molecular level. Clearly, all of this work is geared towards a better understanding of disease origins at the genetic level in order to treat or cure these diseases. However, the use of a “knock-out gas” in the Moscow theatre crisis serves as a powerful reminder that drugs with perfectly legitimate medical applications might be turned to a different use. Although in the Russian case this use was by state authorities, the spread of technologies and knowledge brings such misuse potential well within the reach of sub-state groups like terrorist organizations.

The biotechnology revolution is producing vast amounts of new data, both in relation to genomes that are sequenced and new chemical compounds that are produced by combinatorial means and have to be screened for their properties and potential as new drugs. According to a conservative estimate,[22] more than 1 million such compounds are screened each year in the US alone, 50,000 of which are subsequently eliminated from further consideration because of their toxic properties. Yet developments in this area are progressing rapidly as well: for example, a large-scale chemogenomics database was developed to “enhance and accelerate accurate interpretation of mechanisms of toxicity and pharmacology of chemicals and drugs.” The misuse potential of a system that allows for the identification of new chemical compounds according to their toxicity is obvious.[23] As data mining algorithms become more elaborated,[24] the potential to identify specific toxic effects of chemical compounds and exploit them for malign purposes will increase.

The technology revolution across the life sciences will not only affect drug development but also drug delivery. As one recent review of the field has outlined, “currently, the most potential is offered by pulmonary delivery, i.e. inhalation of drugs to the deep lung.”[25] In order for this to be effective it is necessary to create “drug particles or droplets … in the range [of] 1–5 microns.”[26] This is exactly the particle size that was sought in the weaponisation of known CW and BW agents, making the dual-use aspects of new discoveries in this realm all too clear. The potential of misuse is compounded by the application of nanoparticles, which could either be used to increase the susceptibility of

18 Vogt, G.: Multi-axis robots bring automation to life sciences. In: Industrial Robot: An International Journal 29 (2002), pp. 49-52.
19 Kraljevic, S./Stambrook, P.J./Pavelic, K:Accelerating drug discovery. EMBO reports 5 (2004), pp. 837-842.
20 Sahoo, S.K./ Labhasetwar, V.: Nanotech approaches to drug delivery and imaging. In: Drug Discovery Today 8 (2003), pp. 1112-20.
21 Wood, A./Scott, A.: Combinatorial chemistry picks up speed. In: Chemical Week 162 (9 August 2000), pp. 39-42; Wheelis, M.: Biotechnology and biochemical weapons. In: The Nonproliferation Review 9 (2002), pp. 48-53.
22 Wheelis, M: Biotechnology and biochemical weapons. In: The Nonproliferation Review 9 (2002), pp. 48-53.
23 Ganter, B. /Tugendreich, S. /Pearson, C.I. et al.: Development of a large-scale chemogenomics database to improve drug candidate selection and to understand mechanisms of chemical toxicity and action. Journal of Biotechnology 119 (2005), pp. 219-244.
24 Whittaker, P.A.: What is the relevance of bioinformatics to pharmacology? In: Trends in Pharmacological Sciences 24 (2003), pp. 34-39.
25 Shohet, S./Wood, G.: Delivering biotherapeutics-technical opportunities and strategic trends. In: Journal of Commercial Biotechnology 9 (2002), pp. 59-66.
26 Haystead, J.: New Particle Engineering Technology Improves Drug Solubility’, In: *Pharmaceutical Technology* 27, (2003), no.1, pp. 18-19 and 114.

lung tissue to a CW agent or be directed at specific target tissue in the human body, such as in order to block defence mechanisms.[27]

Similarly, with respect to the BW control regime, S&T developments - such as in the fields of immunology and neurology[28] - are racing ahead. As no control mechanisms exist, the gap between technologies that should be monitored and controlled and actual controls being agreed upon and implemented is widening constantly. If this situation persists for much longer it is questionable whether the political will can be mustered to set up a multilateral system of controls that would actually provide warning of a misuse of cutting-edge life-sciences research.

Around the time of the Fifth BWC Review Conference, several developments in the life sciences occurred that many observers saw as opening wide the door for potential misuse. The “contentious research” in question involved:[29]

- unintentionally potentiating the virulence of the mousepox virus through inserting an IL-4 gene into the mousepox genome;
- synthesis of the poliovirus genome from “chemically synthesized oligonucleotides that were linked together and then transfected into cells”, thereby creating an infectious virus from scratch;[30] and
- potentiation of a potential virulence factor of vaccinia virus, which is of much lower virulence than the smallpox virus and usually used for vaccinations.

Concerns over advances in S&T led the United States National Academies of Science to establish a committee to investigate ways to prevent S&T advances from being misused for hostile purposes.[31] The so-called Fink Committee issued a set of recommendations to address the new environment in which the life sciences are operating and to prevent scientific advances from being misused by states or terrorist groups in BW programmes, while at the same time “enabling legitimate research to be conducted.”[32] The Fink Committee’s recommendations included *inter alia* “self-governance by scientists and scientific journals to review publications for their potential national security risks” and the establishment of a National Science Advisory Board for Biodefense (NSABB) “to provide advice, guidance, and leadership for the system of review and oversight”.[33] Before the publication of the Fink Committee’s report a group of thirty-two journal editors agreed in 2003 on guidelines related to “Scientific Publication and Security”.[34]

The NSABB has been established in the office of the director of the National Institutes of Health.[35] It advises on and recommends “specific strategies for the efficient and effective oversight of federally conducted or supported dual-use biological research, taking into

27 Davis, S.S. 1997, Biomedical applications of nanotechnology-implications for drug targeting and gene therapy. *Trends in Biotechnology*, 15, pp. 217-224.
28 See chapters 3 and 4.
29 See the summaries of the three cases in National Research Council of the National Academies, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology: Biotechnology Research in an Age of Terrorism. Washington, DC: The National Academies Press 2004, pp. 24 -29.
30 Ibid. p. 27.
31 Ibid.
32 Ibid. p. 32.
33 Ibid. pp. 4 -12.
34 Statement on Scientific Publication and Security, reprinted in National Research Council of the National Academies: Biotechnology Research in an Age of Terrorism. Washington, DC: The National Academies Press 2004, pp.98-99.
35 See the NSABB’s website at <www.biosecurityboard.gov/>.

consideration both national security concerns and the needs of the research community."[36] The Board is composed of a maximum of twenty-five voting members whose areas of expertise cover *inter alia* genomics, bacteriology, virology, laboratory biosafety and biosecurity, public health, pharmaceutical production, bioethics, national security, intelligence and law enforcement.[37]

Although these parallel controls of S&T that are increasingly taking shape in the United States point in the right direction, they face the same shortcomings as do the deliberations by BWC states parties in the so-called new process created by the last BWC Review Conference: both of these attempts do not lead to coordinated action on the international level and are thus decoupled from developing the regime as a whole. Moreover, in the area of CW controls some of these measures would have to be taken on board as well. In order to prevent the misuse of twenty-first century chemistry, CWC implementation cannot continue as if the regime existed in a time warp. Otherwise, S&T advances in chemistry, biology and the life sciences in general can be expected to again leave their mark on military thinking and the history of warfare.

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36 United States, Secretary of Health and Human Services: Charter. National Science and Advisory Board for Biosecurity. Washington, DC 2004, dated 4 March, available at <www.biosecurityboard.gov/SIGNED%20NSABB%20 Charter.pdf>.

37 Ibid., p. 2.

3 Assault on Defenses: The Immune System Under Attack

The immune system plays a crucial role in protecting against infectious diseases. This is clearly demonstrated in the case of individuals with genetic defects in certain immune mechanisms, which frequently result in a devastating infectious disease state and eventual death, despite the use of antibiotics or other chemotherapeutic agents. Indeed, the pathogenicity of a microorganism can only rightly be defined within the scope of its interaction with the immune system. To be a successful pathogen, a microorganism must possess strategies that enable it to evade immune defence mechanisms. Immune responses are regulated to a great extent through the production of cytokines, which are bioregulators that can exert both positive and negative effects depending upon the amounts produced. The immune system is thus very vulnerable to both immune evasion strategies and immune bioregulators, a situation that can be easily exploited for good or malign purposes. The central dual use role that the immune system plays in the context of life sciences research can be seen in the examples of research activities that have been frequently quoted in recent years as being potentially extremely dangerous. Most of these examples, including the mousepox experiment[38] and the potentiation of a virulence factor of vaccinia virus[39], involve the exploitation of immune evasion strategies.

In just the past three decades we have witnessed an explosive accumulation of knowledge concerning the mechanisms and functions of the immune system. One area of immunology that has gained enormous importance and developed most rapidly just since the middle 1990s is that of innate immunity. With the discovery of mammalian Toll-like receptors (TLRs)[40] and their importance in governing the recognition of and response to different classes of microorganisms by cells[41] of the innate immune system, research activity in this area of immunology has reached whirlwind proportions.

The special position held by innate immunity relative to the control over infectious diseases can be seen by the fact that the National Institute of Allergy and Infectious Diseases (NIAID) of the US National Institutes of Health (NIH) expanded its program significantly in 2003 to attract immunologists to the area of biodefense research.[42] In this regard, NIAID reported that it “awarded a multi-component grant to create an ‘encyclopedia’ of innate immunity: a comprehensive and detailed picture of this ancient, essential first line of defense against bacterial and fungal diseases”. The stated goal of this undertaking is to gain knowledge that could lead to the development of treatments for infectious diseases. At the same time, however, this information could provide a blueprint for malign attack on the innate immune system.

This chapter will try to show some of the directions that immunology is headed toward and the relevance this might have for future arms control.

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38 Jackson et al. 2001, op. cit.

39 Rosengard, A. M./Liu, Y./Nie, Z./Jimenez, R.: Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement. In: Proceedings of the National Academy of Sciences USA 99 (2002), pp. 8808-8813.

40 Medzhitov, R./Preston-Hurlburt, P./Janeway, C.A., Jr.: A human homologue of the *Drosophila* Toll protein signals activation of adaptive immunity. In: Nature 388 (1997), pp. 394-397.

41 Poltorak, A./He, X./Smirnova, I./Liu, M.Y./Huffel, C.V./Du, X./Birdwell, D./Alejos, E./Silva, M./Galanos, C. et al. 1998, Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in *Tlr4* gene. In: Science 282 (1998), pp. 2085-2088.

42 NIH: NAID biodefense research agenda for CDC category A agents. Progress Report, August 2003. <http://www.niaid.nih.gov/biodefense/research/bioresearchagenda.pdf>.

3.1 Some Pertinent Facts about the Immune System

Characteristic of the immune system is its ability to respond to an invasion of the body by microorganisms or toxic components in ways that afford protection against detrimental effects that could occur. The responses of the immune system include both non-specific (innate immune system) and specific (adaptive immune system) components (Table 3.1). These react in different ways to antigens (chemical components - mainly proteins and polysaccharides), which are substances that can elicit an immune response if they are foreign to the host. Microorganisms are composed of a mosaic of many different antigens. The immune system reacts to these antigens, mounting defence mechanisms that are designed to get rid of the microorganisms. The innate immune system includes components that are present and ready for action even before an antigen challenge is encountered (e.g. phagocytic cells, complement). Some of these components must be activated in order to function, but this activation takes only minutes or a few hours at the most. Macrophages, for example, are phagocytic cells that represent a prominent cellular component of innate immunity. These cells do not recognize antigens in a specific manner but react to classes of antigenic substances from microorganisms called pathogen-associated molecular patterns or PAMPs.

The cellular and molecular components of innate immunity are less specific than those of the adaptive system; that is receptors on macrophages can detect classes of substances and microorganisms, but not uniquely specific structures. For example, many bacteria carry the substance lipopolysaccharide (LPS) on their cell surface. LPS is a classic activator of macrophages. The macrophage recognizes LPS and reacts to this agonist, but it is not able to recognize from which bacterium the LPS comes. Nevertheless, the innate immune system represents the all-important first line of defence against pathogens and is absolutely essential for keeping an infection in check before adaptive immunity can be induced. If innate immunity is malignly attacked, the battle against infections is lost from the start.

Table 3.1. Features of Innate and Adaptive Immunity[a]

Feature	Innate Immunity	Adaptive Immunity
Characteristics		
Specificity for microorganisms	Relatively low (PAMPs)[b]	High (specific antigens)
Diversity	Limited	Large
Specialization	Relatively stereotypic	Highly specialized
Memory	No	Yes
Components		
Physical and chemical barriers	Skin, mucosal epithelia; anti-microbial chemicals e.g. defensins	Cutaneous and mucosal immune systems; secreted antibodies
Blood proteins	Complement	Antibodies
Cells	Phagocytes (macrophages, neutrophils), Natural killer cells	Lymphocytes (B cells that produce antibodies; T cells that carry out cell-mediated reactions)

[a] From A.K. Abbas, A.H. Lichtman, and J.S. Pober, Cellular and Molecular Immunology, 3rd Edition, (Philadelphia: W.B. Saunders Company, 1997)
[b] PAMPs: pathogen-associated molecular patterns

The cellular components of adaptive immunity (B and T lymphocytes) can recognize antigens in a highly specific manner. However, these cells must be driven by antigens to go through different phases of activation and expansion (multiplication of cells) as well as differentiation in order to carry out their functions, e.g. the production of antibodies by B lymphocytes and the destruction of pathogen-infected cells by T lymphocytes. Therefore, adaptive immune responses take days to activate, rather than the minutes or hours required by innate immune responses. Additionally, adaptive immunity has a “memory” that allows a quicker and stronger response the next time that specific pathogen is encountered. Thus, adaptive immunity affords a high degree of specific protection, but it takes time to be induced.

3.2 Immune Evasion Strategies

An area of immunological research that is advancing at an extremely rapid pace is the elucidation of the mechanisms that pathogens use to evade immune defences. In order for a microorganism to be pathogenic, it must have some mechanism(s) that permits it to evade immune defences. There is a great deal of interest in studying these processes with the aim of developing means of countering evasion strategies. At the same time, exploitation of evasion strategies with malign intent should be of particular concern. Some evasion strategies are described below.

3.2.1 Antigenic Variation

Some microorganisms frequently mutate or vary their antigenic composition so that they can no longer be recognized by the antigen receptors of immune system cells. With regard to particular antigens, some microorganisms exhibit a much higher mutation rate than is normal. This is encountered, for example, in connection with the flu virus, the AIDS virus or the causative agent of Lyme disease, *Borrelia burgdorferi*. This is one reason these infectious diseases are resistant to vaccination. In addition, some microorganisms are subject to mutation due to pressures exerted by the immune system itself.[43] In this regard, those antigens that elicit the strongest immune response will be subject to the greatest immune selection pressures.

3.2.2 Regulation of Complement Activity

One of the most important components of immunity is the *complement system*. This is a series of some thirty or so substances in blood serum that become activated in a series of reactions during an immune response.

This is an example of the importance of system balance. Insufficiencies in key components of complement would result in a devastating outcome with regard to certain infectious diseases, despite the use of antibiotics or other chemotherapeutic agents. On the other hand, unrestrained complement activation would cause severe damage to bystander cells. In a healthy body, complement activity is held in check by a variety of regulatory factors, known as regulators of complement activation (RCA).[44]

Members of the poxvirus, herpesvirus and retrovirus families produce substances that mimic RCA proteins and are thus able to escape complement action.[45] The smallpox virus *Variola major* causes a serious, virulent infection in humans, while the virus that is used for vaccination against smallpox, vaccinia virus, usually causes only a very mild or even unapparent infection, at least in individuals with an intact immune system.

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43 Gupta, S./Ferguson, N./Anderson, R.: Chaos, persistence, and evolution of strain structure in antigenically diverse infectious agents. In: Science 280 (1998), pp. 912-915.

44 Goldsby, R.A./Kindt, T.J./Osborne, B.A./Kuby, J.: In: Immunology, fifth edition. New York: W.H. Freeman and Company 2003.

45 Alcami, A./Koszinowski, U.H.: Viral mechanisms of immune evasion. In: Trends in Microbiology 8 (2000), pp. 410-418; Tortorella, D. et al.: Viral subversion of the immune system. In: Annual Review of Immunology 18 (2000), pp. 861-926.

A component of the smallpox virus that may contribute to its pathogenicity or ability to cause disease is the smallpox inhibitor of complement enzymes (SPICE). SPICE has the ability to inactivate one of the key complement components (human C3b) that serves to induce the innate immune process by which cells engulf material which is eventually digested, destroyed or killed. By inactivating the complement activity, a vital area of innate immunity would be disabled. Vaccinia virus also has a complement regulatory protein (called vaccinia virus complement control protein, VCP), which is, however, much less effective (100-fold less) than SPICE. In a recent investigation into the relevance of SPICE in pathogenicity, researchers mutated the VCP gene of vaccinia virus to have the same nucleotide sequence as SPICE.[46] The recombinant mutant VCP proved to be much more efficient than normal VCP in inactivating complement in a test tube reaction. Although the researchers did not actually outfit vaccinia virus with this mutated gene, the work was only one step away from this manipulation. Presumably, vaccinia virus with the mutated gene would be much more pathogenic.

3.2.3 Regulation of Cytokine Activity

Macrophages of the innate immune system produce type I interferons (α and β), which are essential for a successful defence against many viral infections. They are also potent producers of proinflammatory cytokines including interleukin 1 beta (IL-1β), IL-6 and tumour necrosis factor alpha (TNFα), which mediate reactions designed to fight infections. When these cytokines are produced in moderate amounts, they induce mild inflammation reactions and contribute greatly to defence mechanisms directed against pathogens and to the healing process in general. If they are produced in particularly large amounts or continually during chronic illnesses, this can lead to various disorders such as coronary insufficiency, thrombus formation, and in some cases even to shock and death.[47] This makes these activities particularly vulnerable to malign modulation such as by targeting the TLRs to induce hyper-responses, or by inhibiting key components in cellular signalling cascades that would upset the balance.

Anti-interferon strategies are a part of the immune evasion repertoire of most viruses. These mechanisms include the production of soluble versions of interferon receptors, which act as decoys. These decoys bind and inactivate interferons before they reach their “destination” - normal, membrane-bound receptors.[48] Other cytokines, such as IL-2, IL-4, IL-10 and IL-12 (produced by T lymphocytes and macrophages) are essential in directing the activities of different arms of the immune system. One of the most interesting evasion mechanisms identified in recent years is the mimicry of cytokines and cytokine receptors by large DNA viruses (herpesviruses and poxviruses). Cytokine homologues might redirect the immune response for the benefit of the virus, for example by suppressing the anti-viral activity of cytotoxic T cells, as was evidenced in the famous mousepox experiment.[49] Alternatively, viruses that infect immune cells might use these homologues to induce signalling pathways in the infected cell that promote virus replication.[50] Furthermore, soluble cytokine receptors made by the virus might neutralize cytokine activity before the cytokines could react with their normal, membrane-bound receptors.

46 Rosengard et al. 2002, op. cit.
47 Rietschel, E.T./Brade, H.: Bacterial endotoxins. In: Scientific American 267 (1992), pp. 54-61.
48 Alcami/Koszinowski 2000, op. cit.
49 Jackson et al. 2001, op. cit.
50 Alcami & Koszinowski, 2000, op. cit.

3.2.4 Inhibiting Programmed Cell Death

A further immune evasion strategy includes the production of a variety of viral inhibitors of cell death (apoptosis), the so-called programmed cell death. In this regard, apoptosis can be viewed as a response to limit the intracellular propagation of viruses. T Lymphocytes of the adaptive immune system recognize a cell that has been infected by a virus through the presentation by that cell of fragments of viral proteins bound to MHC molecules on the surface of the cell. This recognition leads to the activation of cytotoxic T lymphocytes which attack and kill the cell through the induction of apoptosis.

Some viruses can cause the suppression of the production of MHC molecules. This would mean that viral antigens would not be bound to MHC molecules and could not be recognized by T cells. The cell and therefore the virus production factory would be protected from cytotoxic T lymphocyte destruction.[51] Alternatively, viruses such as cytomegalovirus induce the expression of a certain type of MHC molecule that can bind a receptor on the surface of natural killer cells, inducing suppression of the activity of these cells that are normally an important component of innate immunity.[52]

3.3 Vulnerability of the Immune System to Modulation with Bioregulators

In addition to immune evasion by pathogens, there has to be a great deal of concern about the possibility of modulating immune responses in a negative way with bioregulators that are not microorganisms, but rather substances found normally in the body that regulate biological processes.

The inappropriate production of proinflammatory cytokines can be taken as an example of malign use of bioregulators. Enhancing the proinflammatory cytokine production by using PAMPs to engage Toll-like receptors on the surface of macrophages could at the very least lead to sickness behaviour, which is characterized by fever, drowsiness, lethargy and loss of appetite.[53] However, if the proinflammatory cytokines are produced in particularly large amounts, this could lead to autoimmunity, or eventually even to shock and death.[54] On the other hand, inhibiting the production of these cytokines by using bioregulators that can negatively regulate their synthesis might result in a lack of innate immune protection.

A second example of modulation of immune responses with bioregulators concerns ‘super-antigens’. The immune system is particularly vulnerable to attack by certain super-antigens. Normally, less than 0.01% of B or T lymphocytes respond to a particular antigen. In contrast, a number of super-antigens has been described that can react with a significant proportion of T lymphocytes (between 5–25%).[55]

For example, the bacterial product *Staphylococcus enterotoxin B* (SEB) is a biological agent that also falls into the category of a potential chemical weapon. This toxin was on the

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51 Ibid.

52 Carayannopoulos, L.N./Yokoyama, W.M.: Recognition of infected cells by natural killer cells. In: Current Opinion in Immunology 16 (2004), pp. 26-33.

53 Inui, A.: Cytokines and sickness behaviour: implications from knockout models. In: Trends in Immunology 22 (2001), pp. 469-473.

54 See Rietschel & Brade 1992, *op. cit.*

55 See Goldsby et al. 2003, *op. cit.*

US list of favoured anti-personnel agents as early as 1949[56] and was apparently weaponized by the US Army prior to the negotiation of the BWC.[57] It has also been the subject of extensive research in the biomedical literature. SEB acts as a super-antigen in that it can activate a large proportion of T lymphocytes to produce excessive amounts of cytokines, which can cause systemic reactions including inflammation, fever, widespread blood clotting and shock.[58]

Recently, a B cell superantigen (protein A from the bacterium *Staphylococcus aureus*) has been described that can bind up to 50 % of the B cell population[59], resulting in an increased rate of apoptosis or death of the bound cells. The researchers of this B cell superantigen are considering putting it to therapeutic use.[60] They are engineering the antigens to achieve higher binding affinities and different specificities in order to specifically target malignant B cell populations such as lymphoma and leukaemia.

3.4 Targeted Delivery of Bioregulators

The possibilities for misuse of bioregulators are intricately involved with dual-use aspects of targeted delivery technology. Targeted delivery systems are comprised of components that allow an activity to be targeted to a particular site in the body where that activity is desired. While they may be potentially very useful in vaccine and gene therapy, they can also serve as delivery vehicles for dangerous toxins or bioregulators. There are several potential means of achieving this.

One example of a targeted delivery system are viruses that are used as vectors to transfect a foreign gene into cells for the purpose of immunization or for gene therapy. Infection with the virus would lead to the production of the substance encoded by that foreign gene, for example, a foreign antigen. This is an area of intensive research because of the interest in developing these systems for gene and cancer therapy.[61] Although many questions remain concerning the safety of these systems for therapy purposes,[62] this would presumably be of little concern for a proliferator. A great deal of recent work has been invested in the development of lentivirus (the subfamily of retroviruses to which the AIDS virus belongs) delivery systems, as these viruses are very efficient in infecting cells and achieving stable expression of the transferred genes in those cells. Although lentiviruses normally have a very narrow host range, this can be broadened or altered by a process called pseudotyping.[63] This involves engineering lentiviruses to contain new surface proteins derived from other enveloped viruses that govern the ability of the virus to infect particular cells. This is what is known as changing the tropism of a virus. In any case,

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56 Moon, J.E.v. C.: Chapter 2. The US BW Program: dilemmas of policy and preparedness. In: Wheelis, M./Rozsa, L./Dando,M.R. (eds.): Deadly Cultures: Bioweapons from 1945 to the Present. Cambridge: Harvard University Press (2006).

57 Geissler, E./Lohs, K.: The changing status of toxin weapons. In: Geissler, E. (ed.) Biological and Toxin Weapons Today. Oxford: Oxford University Press (1986), pp. 36-56.

58 See Goldsby et al. 2003, op. cit.

59 Silverman, G.J. et al.: The dual phases of the response to a neonatal exposure to a V_H family-restricted staphylococcal B cell superantigen. In: Journal of Immunology 161 (1998), pp. 5720-5732; Goodyear, C.S./Silverman, G.J.: Death by a B cell superantigen: in vivo V_H-targeted apoptotic supraclonal B cell deletion by a staphylococcal toxin. In: Journal of Experimental Medicine 197 (2003), pp. 1125-1139.

60 Minton, K.: Immune evasion. Germ warfare. In: Nature Reviews Immunology 3 (2003), pp. 442-443.

61 Thomas, C.E./Ehrhardt, A./Kay, M.A.: Progress and problems with the use of viral vectors for gene therapy. In: Nature Reviews Genetics 4 (2003), pp. 346-358.

62 Check, E.: Harmful potential of viral vectors fuels doubts over gene therapy. In: Nature 423 (2003), pp. 573-574.

63 Cronin, J./Zhang, XY/Reiser, J: Altering the tropism of lentiviral vectors through pseudotyping. In: Current Gene Therapy 5 (2005), pp. 387-398.

it is evident that cytokines as bioregulators of the immune system can be delivered quite effectively by viruses engineered to carry the cytokine genes.[64]

Alternatively, molecules can be engineered to contain the toxic portion of a toxin linked to an antigen specific for a particular cell receptor.[65] This antigen would direct the toxin to cells having that receptor. Such engineered molecules are called fusion proteins. As an example, a fusion protein enabling the action of a cytokine (interferon beta, a bioregulator) at sites of inflammation has been constructed.[66]

Aerosolization of vectors carrying foreign genes could represent an effective delivery system, especially if the vector is a virulent microorganism, as most infections begin at the mucosa (mucous membranes). If the bioregulator is not a microorganism, such as in the case of cytokines, super-antigens or fusion proteins, successful delivery by the aerosol route would depend greatly upon the physical and chemical properties of that vector. The US Army in its medical biodefence programme has apparently investigated the absorption of endogenous bioregulators through the aerosol route. It has reported, for example, that the hormone insulin and the proinflammatory cytokine IL-1 were effective in aerosol form in basic pulmonary absorption studies.[67] There is considerable interest in developing better aerosol delivery systems for drug delivery,[68] so that this is an area that should be followed closely. In this context, applications of nanotechnology to improve drug targeting combined with improved methods for absorption are of particular interest.[69] Indeed, there is a growing need to analyze these systems carefully and to assess their applicability for delivering substances to the desired targets in a BW-relevant context.

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64 Jackson et al. 2001 op.cit.
65 Mourez, M./Kane, R.S./Mogridge, J./Metallo, S./Deschatelets, P./Sellman, B.R./Whitesides, G.M./Collier, R.J.: Designing a polyvalent inhibitor of anthrax toxin. In: Nature Biotechnology 19 (2001), pp. 958-961.
66 Adams, G./Vessillier, S./Dreja, H./Chernajovsky, Y.: Targeting cytokines to inflammation sites. In: Nature Biotechnology 21(2003), pp. 1314-1320.
67 USAMRIID: Basic studies seeking generic medical countermeasures against agents of biological origin. In: Annual Report for Fiscal Year 1987, p. 19.
68 Davis, S.S./Illum, L.: Absorption enhancers for nasal drug delivery. In: Clinical Pharmacokinetics 42 (2003), pp. 1107-1128.
69 Davis, S.S.: Biomedical applications of nanotechnology – implications for drug targeting and gene therapy. In: Trends in Biotechnology 15 (1997), pp. 217-224.

4 Malign Misuse of Neuroscience

Only in the last few centuries has the link between the brain and behaviour become clear, and only at the end of the nineteenth century was it demonstrated that the nervous system was made up of billions of separate nerve cells or neurons. We now know that during evolution complex networks of such neurons have developed in order to effect certain behaviours. Whilst the neurons of the central, peripheral and autonomic nervous systems vary enormously in form and function, they can be classed into three broad groups: sensory neurons which convey information into the central nervous system; effector neurons which carry information out of the central nervous system to muscles and other effector organs; and interneurons within the central nervous system which link the sensory and effector neurons and also have links with one another.

Information is conveyed within individual neurons by electrical means - generating nerve impulses which can be recorded and displayed on an oscilloscope. In the twentieth century it was shown that information is conveyed between neurons by chemical means. When a nerve impulse (an action potential) travelling along the long extension or axon of a neuron arrives at a junction (or synapse) with another neuron, it causes the release of a neurotransmitter chemical from the presynaptic cell. This chemical affects the electrical properties of the postsynaptic neuron through its interaction with specialised receptor proteins embedded in the surface membrane of the postsynaptic cell. It has been shown that there are numerous kinds of neurotransmitter chemicals which, depending on the specific receptors involved, can either cause an electrical change which enhances the possibility of an action potential occurring in the post synaptic cell, or, alternatively, decreases that possibility. Various chemical mechanisms ensure that the neurotransmitter is cleared from the synaptic area so that its effect does not persist and so that another action potential in the presynaptic neuron can exert its effect in turn.

This then is the basis for modern insights into how the brain - and therefore behaviour - can be manipulated by chemical means. Clearly, as our understanding of the neuronal circuits underlying specific behaviour increases, and we understand more about the neurotransmitters functioning in such circuits, we have more chance of helping people who are suffering from various malfunctions of the nervous system (mental illnesses). It has to be accepted, however, that such information may be misused by those with malign intent.

Thus in the early years of the east-west Cold War, following the serendipitous discovery of chemical agents (drugs) that could help people with severe mental illnesses, the military took an interest in many different means of chemical incapacitation. The original 1970s study, CB Weapons Today,[70] from the Stockholm International Peace Research Institute (SIPRI) states that the United States Army Chemical Corps drew attention to at least a dozen mechanisms in the late 1950s and it gives details on, for example, hypotension, emesis and disturbance of body temperature and further, lists loss of balance, muscular hypotonia, muscle tremors, and ‘many different psychotropic effects’ on the central nervous system produced by tranquillizers, sedatives, anti-depressants and psychotomimetics. At that time the SIPRI authors argued that there was too little knowledge of the workings of the central nervous system for such central effects to be used successfully to incapacitate. It has been argued since that the genomics revolution of the 1990s will have made a significant difference because the structure of the receptor sub-types affected by relevant neurotransmitter chemicals has increasingly become

70 SIPRI: The Problem of Chemical and Biological Warfare, Volume II of CB Weapons Today. Stockholm: Almqvist and Wiksell 1973, pp. 288-308.

known.[71] It would thus be much easier to design chemical incapacitating agents today to achieve specific effects.[72]

The genomics revolution, however, clearly has much more profound implications for our understanding of biological systems - including those of the central nervous system. As a recent major review noted, the possibility of a systems-level understanding is gaining importance because:

> "[...] progress in molecular biology, particularly in genome sequencing and high-throughput measurement, enables us to collect comprehensive data sets on system performance and gain information on the underlying molecules [...]"[73]

From this viewpoint, what has changed is not just that the genomics revolution has enabled the elucidation of the receptor sub-types involved in central nervous system circuits, but that the molecular mechanisms in whole control systems governing particular behaviours may be elucidated. Another recent review suggested that our increasing ability to understand complex signalling relationships in the central nervous system will enhance the possibility of finding new therapeutic drugs.[74] The attraction of a systems approach combining the expertise of engineers, biologists and mathematicians,[75] while in addition building on the growing capabilities of neuroimaging, is undoubtedly powerful. How far then do we understand how behaviour is controlled by systems within the brain? Great progress is evident in some areas, and brain circuits and neurotransmitter/neuroreceptor functions are being elucidated as the brief following example illustrates.

4.1 Noradrenaline/Arousal

There has been a clear military interest in manipulation of the noradrenaline neurotransmitter system in relation to the arousal level of the central nervous system for some time.[76] That interest apparently continues, one recent report suggesting that drugs affecting the system were "appropriate for immediate consideration as a non-lethal technique".[77]

Noradrenaline is a small-molecule, classical, neurotransmitter which has an unusual distribution in the mammalian central nervous system.[78] The major noradrenaline cell group is the locus coeruleus (LC group). The locus coeruleus contains a surprisingly small number of neurons, some 20,000 in the rat. However, these neurons have axons which

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71 Dando, M.R.: Scientific and technological change and the future of the CWC: The problem of non-lethal weapons. In: Disarmament Forum 4 (2002) pp. 33-44.

72 Dando, M.R.: The Danger to the Chemical Weapons Convention from Incapacitating Chemicals. In: CWC Review Conference Paper No. 4, Department of Peace Studies, University of Bradford (2003) available at <http://www.brad.ac.uk/acad/scwc>.

73 Kitano, H.: Systems biology: A brief overview', Introduction to a special section on systems biology: the genome, ligome and beyond. In: Science 295 (2002), pp. 1662-1664.

74 Davidov, E.J. et al.: Advancing drug discovery through systems biology. In: Drug Discovery Today 8 (2003), pp. 175-183.

75 Henry, C.M.: Systems biology: Integrative approach to drug discovery. In: Chemical and Engineering News 19 May 2003, pp. 45-55.

76 Dando, M.R.: Chapter 8, An Assault on the Brain. In: A New Form of Warfare: The Rise of Non-Lethal Weapons. London: Brassey's (1996), especially pp.136-168.

77 Lakoski, J.M. et al.: The Advantages and Limitations of Calmatives for Use as a Non-Lethal Technique. Applied Research Laboratory, College of Medicine, Pennsylvania State University, (2000).

78 Longstaff, A.: Instant Notes: Neuroscience, 2nd Edition. New York: Taylor and Francis 2005.

branch profusely in the brain, so noradrenaline acts as a neurotransmitter in many different brain regions.

Not surprisingly, noradrenaline transmission is involved in many brain functions, including "arousal, vigilance, learning and memory.[79] Extensive studies in rats, cats and monkeys have elucidated much of how this system functions in arousal and vigilance.[80]

Though the detailed operations of this noradrenaline system are complex, and though it may have greater involvement in vigilance than just with arousal levels, one simple point is of particular interest to those with malign intent. The noradrenaline neurons have autoreceptors that are inhibitory: production of noradrenaline limits its own production.[81] Thus it has been found that drugs which affect such receptors in the same way as the noradrenaline natural transmitter (agonists) will, if given in sufficient quantity, put the animal (or human) to sleep. Not surprisingly, one military report in the early 1990s noted that such compounds "have been considered to be ideal next generation anesthetic agents which can be developed and used in the Less-Than-Lethal [Non-Lethal] Technology Program.[82]

It is obvious in that regard that increasing understanding of receptors and their sub-types becomes important. It has been known for over 50 years that there are two broad classes of receptors for noradrenaline termed α- and β-adrenoceptors, both of which are slower-acting G protein-coupled receptors (GCPRs) located on cell membranes. The coming of molecular biology allowed the genes for six human α-adrenoceptors to be identified (α_{1A}, α_{1B}, α_{1D} and α_{2A}, α_{2B} and α_{2C}).[83]

Studies are now in progress to elucidate the nature of numerous polymorphisms in the nine different sub-types of human α- and β- adrenoceptors and the role, if any, these play in various diseases.[84]

4.2 Investigation of the Possibilities

There are many examples in the current literature that amply demonstrate how different the present capabilities are in comparison to those of the 1950s. The following are therefore only illustrative of the dangers.

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79 Editorial: New vistas for an old neurotransmitter. In: Biological Psychiatry 46 (1999), pp. 1121-1123. (Introduction to a special issue covering pages 1121-1320).

80 Aston-Jones, G. et al.: Role of locus coeruleus in attention and behavioural flexibility. In: Biological Psychiatry 46 (1999), pp. 1309-1320.

81 Fernandez-Pastor, B./Meana, J.J.: In vivo tonic modulation of the noradrenaline release in the rat cortex by locus coeruleus somatodendritic alpha2 adrenoceptors. In: European Journal of Pharmacology 442 (2002), pp. 225-229.

82 Edgewood RDEC: Scientific Conference in Chemical and Biological Defense Research: Abstract Digest. US Army Chemical and Biological Defense Command, Aberdeen Proving Ground, Maryland, 1989-94.

83 Docherty, J.R.: Subtypes of functional α_1- and α_2-adrenoceptors. In: European Journal of Pharmacology, 361 (1998), pp. 1-15.

84 Small, K.M. et al.: Pharmacology and physiology of human adrenergic receptor polymorphisms. In: Annu. Rev. Pharmacol. Toxicol. 43 (2003), pp. 381-411.

4.2.1 Post-Traumatic Stress Disorder (PTSD)

The human species has evolved mechanisms to ensure that dangerous events are well remembered for the obvious good reason. If this response gets out of hand we call it post-traumatic stress disorder (PTSD). It clearly causes great distress to those who suffer from PTSD, and it is not too difficult to discern that the condition involves at least two components: learning and memory."[85] We are clearly dealing here with learning about aversive events and consolidation of the memory of such aversive events. The basic elements of the system for dealing with fearful events is built into all mammals.

If we are in a wood and see a stick that might possibly be a snake we are better reacting immediately as if it were indeed a snake. However, while the amygdala pathway prepares for action, the cortex pathway is simultaneously processing the information, and if it decides that what is seen is actually a stick and not a snake little effort is wasted as it can switch off the emergency response.

However, the amygdala is involved not only in "the acquired association of cues with emotional responses, especially the autonomic and motoric responses elicited by fear", but it also "mediates the consolidation of long-term explicit memories of emotionally arousing experiences by influencing other brain regions involved in memory consolidation."[86] It is this second process of memory consolidation that is surely of more interest in relation to PTSD.

Details of the neurotransmitter and neuroreceptor systems and circuits involved in the various pathways linked to the amygdala's role in memory consolidation are being steadily elucidated.[87] The system is very complex[88] and is, as yet, far from completely understood. Enough is known, however, to suggest that systems biologists will decipher it rather quickly.

The idea of a direct relationship between noradrenaline and memory for emotional events has been tested in humans. Healthy subjects were either given a placebo or propranolol (which passes the blood brain barriers and antagonises the action of noradrenaline) one hour before viewing a series of either neutral or emotionally stressful scenes. One week later people who had received the placebo had significantly better memories of the emotional slides but those who had received the propanolol did not remember them any better than the neutral ones.[89]

Dr. Leon Kass, chairman of the President's Council on Bioethics in the United States has been quoted as saying that propranolol is „the morning-after pill for just about anything that produces regret, pain, or guilt."[90] Also, a national co-ordinator for "Vietnam Veterans Against the War" agreed and argued that such treatment could "make men and women do anything and think they can get away with it". A different possibility, of course, is that those with malign intent might find means - through a chemical agent - to enhance PTSD, not prevent it.

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85 Longstaff 2005, op.cit.

86 McGough, J.L. et al: Amygdala modulation of memory consolidation: Interaction with other brain systems. In: Neurobiology of Learning and Memory 78 (2002), pp. 539-552.

87 Ferry B. et al.: Basolateral amygdala noradrenergic influences on memory storage are mediated by an interaction between β- and α_1-adrenoceptors. In: Journal of Neuroscience 19 (1999), pp. 5119-5123; Roozendaal, B.: Glucocorticoids and the regulation of memory consolidation. In: Psychoneuroendocrinology 25 (2000), pp. 213-218.

88 Vermetten, E./Bremner, J.D.: Circuits and systems in stress: I. Preclinical studies. In: Depression and Anxiety 15 (2002), pp. 126-147.

89 Southwick, S.M. et al.: Role of norepinephrine in the pathophysiology and treatment of post-traumatic stress disorder. In: Biological Psychiatry 46 (1999), pp. 1192-1204.

90 Baard, E.: The guilt-free soldier: New science raises the spectre of a world without regret. In: The Village Voice 22-28 January (2003).

We can initially conclude that the new systems biology brought about by the genomics revolution and associated scientific advances will undoubtedly open up complex behavioural systems not only to benign but also to malign manipulation. In considering the latter therefore, we have to ask just what might soon be open to manipulation.

4.2.2 Reassessing Cold War Research

An initial approach to a more systematic investigation of the possibilities clearly is to look back at what was done in the Cold War period. It is important not to underestimate the scientific effort involved in that period. For example, a United States General Accounting Office report of 1994[91] noted that from 1952 to 1975 the Army carried out a classified medical research programme to develop incapacitating agents that involved 7,120 Army and Air Force personnel.

The original SIPRI study[92] quoted a US Army manual of 1968 in which it was argued that only two types of chemical agents aimed at the central nervous system were likely to be encountered in military use: CNS depressants (such as BZ, cannabinols and phenothiazine), which sedate and destroy motivation, and *CNS* stimulants (such as LSD), which cause excessive nervous activity, making concentration difficult and causing the inability to act in a sustained, purposeful manner.

There is no mention of the disruption of peptide neurotransmission here but this is not surprising since understanding of this phenomenon would only come later.

However, by the 1990s there was definite military interest in the potential misuse of neuropeptides, as is evident from a 1990 US Army Intelligence Agency report[93] on incapacitating agents research in European communist countries.

The 1997 US Army textbook, Medical Aspects of Chemical and Biological Warfare, drawing on the work carried out between the early 1950s and early 1970s, suggests that virtually all psychochemicals can be classified into four groups: stimulants; depressants; psychedelics; and deliriants. It suggests that the drugs of interest pass the blood-brain barrier with ease and exert their dramatic effects on the functions of the central nervous system.[94]

Thus the textbook concludes that it is possible to disrupt these higher functions with lower amounts of agent than those that are required to produce lethal effects.

In the United States opioids related to the fentanyl derivative used in Russia to end the Moscow theatre hostage crisis in 2002 were still being researched in the early 1990s, as were agents that could affect α_2-adrenergic transmitter/receptor systems.[95] Also, central nervous system processes related to circadian rhythms of sleep and alertness are increasingly being manipulated by the military - for example, so that pilots are fit to carry

91 Conahan, F.C.: Human Experimentation: An Overview on Cold War Era Programs, Testimony before the Legislative and National Security Subcommittee, Committee on Government Operations, House of Representatives, September 28th. GAO/T-NSIAD-94-266. Washington, D.C.: General Accounting Office 1994.

92 SIPRI 1973 The Problem of Chemical and Biological Warfare*,* op.cit., pp. 302-303.

93 US Army Intelligence Agency: Letter Report: Incapacitating Agents, European Communist Countries, AST-1620R-100-90, US Army Foreign Science and Technology Center, 16 July 1990.

94 Ketchum, J.S./Sidell, F.R.: Incapacitating Agents. In: Sidell, F.R./Takafuji, E.T./Franz, D.R. (eds), Medical Aspects of Chemical and Biological Warfare. Washington, DC: Office of the Surgeon General (1997), pp.287-306.

95 Dando, M.R. 1996, op.cit., pp.136-168.

out extended missions.[96] Of course, a great deal more is now known about the systems biology of circadian rhythms in mammals, thus opening them up to malign manipulation in many ways.[97] Though sometimes forgotten, the technology of drug delivery has also been revolutionised in recent decades as the pharmaceutical industry seeks more effective means of drug discovery. It follows that this necessarily also impacts on the possibilities for malign manipulation.[98]

Neuroscientists have always placed a strong emphasis on understanding systems. It is therefore no surprise to see neurobiology examples being cited in current reviews of the new systems biology.[99] A final reason for keeping an open mind and a broad approach, of course, is the scope and pace of change in the biological sciences in general at the present time.

What follows is therefore best considered illustrative rather than in any way definitive of the problems we may face.

4.2.3 The Central Nervous System

Before investigating two more detailed examples of potential misuse, it is necessary first to describe something of the structure of the human nervous system. This is divided into the central nervous system (brain and spinal cord) and the peripheral nervous system.[100] Information from peripheral sense organs is received via afferent pathways and processed within the central nervous system. Output from the central nervous system is sent via efferent pathways to the somatic nervous system (muscles) and to the autonomic nervous system (heart, gut, glands etc.).

The most useful way to understand this massively complex structure is by reference to its growth during development. As the embryo develops, there are at first three primary brain regions: the prosencephalon (forebrain); the mesencephalon (midbrain); and the rhombencephalon (hindbrain). Within a few weeks the forebrain and hindbrain each divide in two. The forebrain gives rise to the telencephalon and diencephalon while the hindbrain gives rise to the metencephalon and the myelencephalon. The telencephalon of the forebrain then develops into the cerebrum with its hugely expanded, characteristic, cerebral hemispheres which cover the top and side surfaces of the brain (Table 4.1). The surface of the cerebrum is made up of central nerve cells in areas such as the primary motor and somatosensory cortex regions. Other central nerve cells are grouped in deeper structures often called *nucleii* or *ganglia*. There are also large regions of connecting nerve fibres throughout the brain (termed white matter because of the colour of the sheathing around the nerve fibres). In general, it can be said that the parts of the brain nearer the spinal cord deal with more automatic functions (such as heart and temperature control)

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96 Knickerbocker, B.: Military looks to drugs for battle readiness: As combat flights get longer, pilot use of amphetamines grows, as do side effects. In: The Christian Science Monitor (9 August 2002).

97 Dyk, D.-J./Lockley, S.W.: Functional genomics of sleep and circadian rhythm. In: J. Appl. Physiol. 92 (2002), pp. 852-862; Wang, G.K./Sehgal, A.: Signalling components that drive circadian rhythms. In: Current Opinion in Neurobiology 12 (2002), pp. 331-338; Van Gelder, R.N. et al.: Circadian rhythms: In the loop at last. In: Science 300 (2003), pp.152-153.

98 Dando, M.R.: The New Biological Weapons: Threat, Proliferation and Control Boulder, CO: Lynne Rienner 2001, pp.103-116.

99 Ideker, T./Galitski, T./Hood, L.: A new approach to decoding life: Systems biology. In: Ann. Rev. Genomics Hum. Genet. 2 (2001), pp. 343-372.

100 Dando, M.R.: Chapter 6, The Human Nervous System. In: A New Form of Warfare: The Rise of Non-Lethal Weapons. London: Brassey's (1996).

and that higher functions are located more in the forebrain.[101] Some of the larger structures in the brain which are mentioned later in this chapter are listed in Table 4.1.

Table 4.1 Some structures of the brain*

FOREBRAIN (Proencephalon)
Telencephalon
Cerebral cortex
- Archicortex
- Hippocampus
Basalganglia
- Amygdala
- Striatum
Diencephalon
Hypothalamus
Thalamus
MIDBRAIN (Mesencephalon)
Tectum
HINDBRAIN
Metencephalon
Cerebellum
Pons
Myencephalon
Medulla oblongata

* From Dubin, How the Brain Works

101 Dubin, M.W.: How the Brain Works. Oxford: Blackwell 2002.

4.2.4 Brain Cholinergic Systems

The central nervous system is made up of billions of individual nerve cells (neurons). Transmission of information within a neuron is by electrical means and the transmission of such nerve impulses can be recorded with suitable equipment. However, most transmission of information between neurons or between neurons and effector systems (muscles, for example) is by chemical means. The first chemical neurotransmitter to be discovered was acetylcholine, a small molecule. Subsequently, many other small molecule neurotransmitters, such as noradrenaline and dopamine, have been discovered. More recently, it has been discovered that various neuropeptides also function as neurotransmitters and that sometimes a particular neuron can employ both a small molecule neurotransmitter and a neuropeptide at the same time.

What is of interest here is that the nerve agents weaponised as lethal agents in past offensive programmes interfered with acetylcholine's functions in what are termed *cholinergic* transmission systems. There are two distinct types of cholinergic synapse, a synapse being a junction between presynaptic and postsynaptic nerve cells where information is transferred. At one of these types of synapse the effect of acetylcholine can be mimicked by nicotine and at the other it can be mimicked by muscarine, a chemical extracted from a mushroom. Despite such differences, the acetylcholine produced at all cholinergic synapses is destroyed by an acetylcholinesterase enzyme so that its effects are not prolonged.

The weaponised nerve agents were found to bind to acetylcholinesterase and thus to inhibit its action. Consequently, cholinergic synapses were flooded with acetylcholine and death from the consequent malfunction of essential body systems quickly followed.[102]

The incapacitating agent BZ, which was also weaponised by the United States in the 1960s, interferes with the operation of acetylcholine at muscarinic synapses in a different way. BZ locks onto the receptors of the postsynaptic cell in this type of synapse and so prevents acetylcholine exerting its normal effects.[103] As most of the cholinergic synapses in the brain are of the muscarinic type, BZ was found to have severe effects on behaviour (Table 4.2). It does not appear, however, that BZ was ever used in warfare. This is hardly surprising because the effects were too wide-ranging to be predictable in any particular individual. The question here is whether advances in neuroscience have produced a situation in which more controllable changes in behaviour could be produced.

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102 Sidell, F.R.: Nerve Agents. In: Sidell, F.R./Takafuji, E.T./Franz, D.R. (eds), Medical Aspects of Chemical and Biological Warfare. Washington, D.C.: Office of the Surgeon General, US Army (1997), pp.129-180.

103 Ketchum/Sidell 1997, op.cit.

Table 4.2 Effects of BZ on human beings[a]

Rapid pulse
Dry mouth and blurred vision
Poor co-ordination
Restless activity
Stupor
Confusion, incoherence, hallucinations, disorientation
Irritable, suspicious and uncooperative
Inability to solve problems or remember information

[a] From Dando, *A New Form of Warfare*[104]

Nicotinic receptors act by the transmitter simply opening a pore in the post-synaptic neuron membrane and thus allowing a flow of ions which changes the electrical characteristics of that cell. Muscarinic receptors operate differently. These act via various G-proteins to change both the electrical and more complex metabolic activities of the post-synaptic cell. To date, five different muscarinic receptor sub-types (M_1-M_5) have been discovered.[105] The odd numbered muscarinic receptors excite the post-synaptic cell whilst the even-numbered receptors decrease its electrical activity.

As the revolution in the life sciences has progressed, it has become possible to breed different strains of mice each lacking one of the different sub-receptor types (so-called 'knockout mice') and to discover where the different sub-types are to be found in the brain and what their different functions are in these different locations.[106] The inhibitory receptors may be located on the presynaptic neuron and function there as inhibitory autoreceptors. Such results are obviously of great interest to those trying to help people with Alzheimer's disease.

If a selective agonist could be found for the M_1 receptor it might be possible to increase the level of excitation in the cortex and make up for the deficiency in acetylcholine, but this approach has not proved to be successful. Another possibility is to find a selective antagonist to the M_2 receptor and thus to block the inhibition of the presynaptic cell and increase the production of acetylcholine back to functional levels.

Several drug companies are pursuing this strategy.[107] Clearly, however, it could also be possible to find a chemical which acted in such a way as to be more effective agonist at M_2 receptors than the natural transmitter. Such a chemical might therefore provide a

104 Dando, M.R. 1996, op.cit., especially Chapter 6.
105 Felder, C.C. et al.: Therapeutic opportunities for muscarinic receptors in the central nervous system. In: J. Medical Chemistry 43 (2000), pp. 4333-4353.
106 Bymaster F.P. et al.: Use of M1-M5 muscarinic receptor knockout mice as novel tools to delineate the physiological roles of the muscarinic choliergic system. In: Neurochem. Res. 28 (2003), pp. 437-442.
107 Lachowicz, J.E. et al.: Discovery of SCH211803, a high affinity, selective M2 receptor antagonist and a novel approach to treatment of Alzheimer's disease. In: Soc. Neurosci. Abstr. 27 (2001), p. 679.

specific disruption of function instead of the multiple and unpredictable disruption caused by BZ.

So far we have discussed something of the neurobiology of awareness, fear, and cognition. But these higher functions rest on a whole set of more automatic homeostatic functions. These kinds of functions are normally regulated from centres in lower parts of the brain near the junction with the spinal cord. In a more comprehensive treatise of this chapter[108] we consider a further aspect of one regulatory system – sleep – and, in particular, one of its manifestations, narcolepsy.

108 Kelle et al. 2006, op. cit.

5 Malign Manipulation of the Neuroendocrine-Immune System

Concerns about biological weapons and biological terrorism have increased over the last decade and especially since the events of 11 September 2001 in the United States. There has been a growing belief that large-scale biological weapons attacks are becoming more likely.[109] The medical profession has been amongst those groups which have devoted more and more attention to what might need to be done in the event of an attack.

If standard accounts of the effects of well-known biological weapons agents are reviewed - like those of agents on the Centers for Disease Control (CDC) Category A list such as smallpox, anthrax, plague, botulism, tularemia and viral hemorrhagic fevers - it becomes very apparent that easy diagnosis of the cause of any such attack would be far from straightforward.[110] If people had fallen victim to any one of a number of different biological weapons agents on the Category A list, they would often present with the same "flu-like" symptoms. This would also be true for some of the lesser agents on the Category B and C lists.

Not surprisingly, medical specialists have begun to consider how their particular expertise might be best used to assist in patient diagnosis and better care. It has been argued that neuroscience is one of the specialties that can be recruited to help deal with a biological weapons attack should such an event occur. [111]

The connection between neuroscience and possible biological attacks with classical agents may not be readily apparent to the general public**,** but the connection with immunology is perhaps less surprising. The body's immune system is its defence mechanism, so when the victim of an attack begins to be affected by an invading micro organism it is to be expected that the defence mechanism will be activated. What may still be a surprise is that microorganisms have evolved means by which to invade or even to attack the defensive immune system itself. Several examples of this have been presented in Chapter 3.

The interactions between potential biological weapons agents and the immune and nervous systems can be extremely complex. This is well illustrated by the case of the Category B - but previously weaponised - incapacitating staphylococcal enterotoxin B (SEB).[112] Although this was probably not clear when the toxin was weaponised by the United States in its early Cold War offensive biological weapons programme, SEB exerts its incapacitating effects through a particular action on the adaptive immune system (see chapter 3). The toxin was particularly attractive to weaponeers because of the very low dose required to incapacitate:

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109 Karwa, M. et al.: Bioterrorism: Preparing for the impossible or the improbable. In: Critical Care Medicine 33 (2005), pp.575-595.

110 For an overview of the three lists see <http://www.bt.cdc.gov/agent/agentlist-category.asp>.

111 Prakosh, K.M./Lo, Y.L.: The role of clinical neurophysiology in bioterrorism. In: Acta Neurol. Scand. 111 (2005), pp. 1-6.

112 Ulrich, R.G. et al.: Staphylococcal enterotoxin B and related pyrogenic toxins. In: Sidell, F.R. et al. (eds), Medical Aspects of Chemical and Biological Warfare. Washington DC: Office of the Surgeon General, US Army (1997), pp.621-630.

> "[...] The dose that is incapacitating for 50% of the human population exposed (also called the effective dose [ED_{50}]) was found to be 0.0004µg/kg, and the dose that is lethal for 50% of the human population exposed (LD_{50}) was estimated to be approximately 0.02µg/kg, both by the inhalation route." [113]

The effective dose, though much lower than that required for synthetic chemicals, was additionally much smaller than the lethal dose. This fact made the toxin more potentially usable for incapacitation.

The impact of administration of the toxin, however, is not confined to the immune system. It has recently been demonstrated that there are also quite significant changes induced in the endocrine (hormonal) and nervous systems and even behavioural changes. It has been shown that administration of SEB activates the hypothalamus-pituitary-adrenal (HPA) stress response axis.[114]

5.1 Neural Regulation of the Immune System

In order to survive, living organisms have to maintain a relatively stable internal environment. This stability is threatened by both internal factors, such as a disease process, and external factors such as stress. Human and animal bodies have therefore evolved complex regulatory (homeostatic) mechanisms which counteract such disruptive factors and re-establish the internal stable state.

Of interest here is how the nervous system responds to *stress*, as was briefly described in Chapter 4. The central nervous system can impact on the immune system in two ways, via:

> "[...] (a) the hormonal stress response and the production of glucocorticoids, and (b) the autonomic nervous system with the release of noradrenaline [...]" [115]

The central nervous system can also affect the immune system through the peripheral release of neuropeptides but that issue will not be addressed here. What is of particular interest is the brain's response to stressors through the hypothalamus producing corticotropin-releasing hormone (CRH, also referred to as corticotropin-releasing factor or CRF), which stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH), which in turn causes the adrenal gland to secrete the immunosuppressant glucocorticoids. Whilst the mechanism is clearly complex, with many other feedback loops being involved,[116] this hypothalamus-pituitary-adrenal (HPA) axis is the essential element for our purposes here. The total HPA general adaptive response can also be activated by immune cytokines (such as interleukins) produced in reaction to pathogens. Then, as in response to stress, the glucocorticoids eventually generated inhibit the further production of such cytokines.

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113 Ibid.
114 Pacheco-Lopez, G. et al.: Behavioural endocrine immune-conditioned response is induced by taste and superantigen pairing. In: Neuroscience 129 (2004), pp. 555-562.
115 Webster, J.I./Tonelli, L./Sternberg, E.M.: Neuroendocrine regulation of immunity. In: Ann. Rev. Immunol. 20 (2002), pp. 125-63.
116 Sternberg, E.M.: The stress response and the regulation of inflammatory disease. In: Annals of Internal Medicine 117 (1992), pp. 854-66.

There is now an accumulation of evidence which shows that deregulation of this system can cause a variety of diseases. As a background paper from the US National Institutes of Health summarised recently:

> "Ideally, stress hormones damp down an immune response that has run its course. When the HPA axis is continually running at a high level, however, the damping down can have a downside, leading to decreased ability to release the interleukins and fight infection. […] Conversely, there is evidence that a depressed HPA axis, resulting in too little corticosteroid, can lead to a hyperactive immune system and increased risk of developing autoimmune diseases - diseases in which the immune system attacks the body's own cells [...]" [117]

This evidence comes from a very wide range of sources. For example, subjecting animals to quite modest levels of stress can greatly affect their ability to fight bacterial infection of cutaneous injuries.[118]

At a different level, there is much evidence of the impact of the nervous on the immune system in humans.[119] Even short-term stress can have an effect. For example, students sitting examinations were found to have a significantly slower (40%) rate of healing of a wound on the hard palate if the wound was made three days before an examination than if it was made in the same individuals during the summer vacation. Interleukin-1 levels - an important indicator of immune function - were also substantially lower during the examination period.

Stress is also involved in the modulation of the immune responses through mechanisms involving the neurotransmitter serotonin. This is a biologically active amine that plays a prominent role in the regulation of processes such as mood, appetite and sleep. During neurotransmission, serotonin is released from neurons into the synaptic cleft between cells. The amount of serotonin available for neurotransmission in the synaptic cleft is regulated largely by the serotonin transporter involved in the reuptake of serotonin after it has been released.[120]

In this regard it is also becoming clear that there are individual differences at the genetic level which can have a major bearing on response to stress. One recent study reported on 847 white New Zealanders who had been tracked from birth in the early 1970s through to adulthood.[121] It had been found that there are two forms of the gene for the serotonin transporter. The two versions are labelled short and long and of the people studied 17 per cent had two copies of the short version, 31 per cent had two copies of the long version and 51 per cent had one copy of each. Startlingly, the researchers found that having one or two copies of the short version had a pronounced behavioural impact:

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117 National Institutes of Health: Stress system malfunction could lead to serious, life threatening disease. In: NIH Backgrounder (9 September 2002), available at <http://www.nih.gov/news/pr/sep2002/nichd-09.htm>.

118 Rojas I.G. et al.: Stress-induced susceptibility to bacterial infection during cutaneous wound healing. In: Brain, Behaviour and Immunity 16 (2002), pp. 74-84.

119 Kiecolt-Glaser, J.K. et al.: Psychoneuroimmunology: psychological influences on immune function and health. In: Journal of Consulting and Clinical Psychology 70 (2002), pp. 537-47.

120 Kubera, M./Maes, M.: Serotonin-immune interactions in major depression. In: Patterson, P./Kordon, C./Christen, Y. (eds.), Neuro-Immune Interactions in Neurologic and Psychiatric Disorders. Berlin: Springer (2000), pp. 79-87; Gordon, J./Barnes, N.N.: Lymphocytes transport serotonin and dopamine: agony or ecstasy? In: Trends in Immunology 24 (2003), pp. 438-443.

121 National Institutes of Health: Gene more than doubles risk of depression following life stresses. In: NIH News Release (17 July 2003), available at <www.nimh.nih.gov/events/prgenestress.cfm>.

> “Among people who suffered multiple stressful life events over 5 years, 43 percent with one [the short] version of the gene developed depression, compared to only 17 percent with [the long][...] version of the gene [...]”[122]

It was also found that people with only the long version of the gene were no more subject to depression - no matter how many stressful events they experienced - than those totally spared stressful events.

The gene involved has a slight variation in a region which acts to control the switching on and off of transporter protein production. The short variant makes less protein and therefore there is a longer binding and function of the serotonin neurotransmitter before it is cleared from the synapse. Significantly, hypothalamic corticotropin-releasing hormone neurones are known to receive a positive input from serotonin neurones.[123] Severe depression, of course, resembles a chronic stress response with production of high glucocorticoid levels possibly being responsible for lower immune system functions.[124]

5.1.1 Malign Manipulation?

The question then is how might such an increased level of understanding of these interactions be misused by those intent on causing harm? Given the complexity of the interactions, there could be many possibilities. One obvious possibility which stands out in the literature is the link between the disruption of metabolism and frailty in old age.

Frailty is not a simple characteristic to define, but it clearly includes factors such as loss of muscle strength and weakness, limited mobility, being underweight and failing to use nutrients effectively.[125] There appears to be a strong link between high levels of circulating interleukin 6 (IL-6) and frailty. IL-6 plays a role in many diseases that are major contributors to disability in the elderly, such as coronary heart disease, stroke, congestive heart failure, osteoporosis, arthritis, depression and dementia.[126]

Not surprisingly, given such findings, IL-6 is not normally detected in the serum of healthy young individuals unless there is trauma, infection or stress. Then, IL-6 is expressed and contributes to typical inflammatory processes. If IL-6 levels are increased in healthy individuals it is very likely that this would have severe effects. From our point of view here it is interesting to note that glucocorticoids have been shown to inhibit IL-6 production in a range of different tissue types. The gene is regulated via a number of routes including corticosteroid interaction with the glucocorticoid receptor (GR) leading to the binding of the IL-6 promoter and thus to inhibition of the gene. Theoretically at least, one could consider the possibility of an irreversible blockage of the GR preventing such inhibition and leading to continuous overproduction of IL-6 with the consequent disablement of those affected - even the young and healthy.

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122 Ibid.
123 Sternberg 1992, op.cit.
124 Harvard Mental Health Letter: The mind and the immune system. April 2002, available at <http://www.health.harvard.edu/medline/mental/M0402a.html>.
125 Hamerman, D.: Toward an understanding of frailty. In: Annals of Internal Medicine 130 (1999), pp. 945-50.
126 Ferrucci, L. et al.: Serum IL-6 level and the development of disability in older persons. In: J. Am. Geriatric Soc. 47 (1999), pp. 639-46.

5.1.2 Molecular Mechanisms

At the beginning of this chapter we referred to the work of the US National Institutes of Health. In a summary of the work of the NIH section on Neuroendocrine Immunology and Behaviour the chief of the section, Esther Sternberg, summarised the different levels of analysis being carried out. These ranged from the systems level (e.g. neuroendocrine responses) to the neuroanatomical level (e.g. peptide expression in the brain) through the cellular level (e.g. hypothalamic cell neurohormone and neuropeptide production) to "[...] the molecular level (glucocorticoid receptor, estrogen receptor, other nuclear hormone receptors, cytokine and cytokine receptors) [...]" [127]

It is, of course, at this molecular level that the current mechanistic approach to biology brings the greatest possibilities for knowledge that can be used for good in medicine or ill in hostile applications. As noted in previous chapters, what is of particular importance is the impact of the genomics revolution on our understanding of cellular receptors and receptor mechanisms in response to intercellular signalling molecules. There is obviously considerable medical interest in glucocorticoids because of their wide range of physiological functions both in relation to the stress response and a range of other vital endocrine functions. Researchers therefore face the problem of finding selective drugs which will activate one function only without causing side-effects due to other functions. Additionally, as well as glucocorticoid receptors there are other steroid hormone receptors which can react to the same glucodorticoids and therefore cause further effects. Consequently, "the identification of more selective functional ligands remains a goal of clinical and pharmaceutical research."[128]

The understanding of corticotropin-releasing factor (CRF) and CRF receptors has also undergone remarkable development in recent years.[129] CRF receptors, of course, belong to the class of G protein-coupled receptors and are two types, CRFR1 and CRFR2. It has been found that CRF itself has a ten-fold higher affinity for CRFR1 over that for CRFR2. The tissue distribution of the two receptor types in the brain appears to be rather clearly related to their physiological functions, with CRFR1 being located in anterior pituitary corticotropes and being stimulated by CRF to activate the release of ACTH. There is another burgeoning line of research activity which strongly suggests involvement of CRF and associated ligands and receptors in anxiety behaviours and depression.[130]

What is important to note is that our increasing understanding of molecular mechanisms (derived from the genomics revolution) is allowing a very rapid accumulation of new knowledge which may be used for benefit or for hostile purposes.

5.2 Immune Regulation of the Nervous System

Infection is one of the main natural stimuli for modulation of the nervous system by the immune system. In this way, the immune system signals to the brain that there is a present danger of infectious microorganisms. Signalling is accomplished in one primary manner

127 Sternberg, E.M.: SNIB: Section on Neuroendocrine Immunology and Behavior 2003. Available at <http://intramural.nimh.nih.gov/snib/>.
128 Coghlan, M.J. et al.: Selective glucocorticoid receptor modulators. In: Annual Reports in Medicinal Chemistry 37 (2002), pp. 167-75.
129 Bale, T.L./Vale, W.W.: CRF and CRF receptors: Role in stress responsivity and other behaviours. In: Ann. Rev. Pharmacol. Toxicol. 44 (2004), pp. 525-57.
130 Ibid.

through the action of proinflammatory cytokines (cytokines causing inflammation reactions) such as interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNFα) and IL-6, which are produced by cells of the immune system (primarily macrophages) after contact with microorganisms or their products.[131] The cytokines gain entry into the circulation from sites of the immune response in tissues and organs, and subsequently trigger reactions in the brain collectively known as sickness behaviour, which is characterized by fever, drowsiness, lethargy and loss of appetite.[132]

The mechanism of fever induction has been studied most extensively. The brain is protected from the potentially harmful effects of biologically active substances or cells in the circulation by the blood-brain barrier, which is manifested by the extremely tight junctions between the endothelial cells lining blood capillaries[133] that prevent circulating substances of a particular size and chemical property (as well as cells) from entering the brain. Proinflammatory cytokines are of a sufficiently large size that makes it unlikely that they can pass the blood-brain barrier. However, numerous pathways to explain how cytokines produced in the periphery can influence central nervous system events have been studied. For example, highly localized windows in this barrier known as circumventricular organs, which are sites that have blood capillaries with open junctions, allow passage of cytokines from the circulation into the brain. Evidence suggests that such windows are located in the anterior area of the hypothalamus.[134]

The cytokines entering the brain at this point bind to their receptors on cells in this area of the hypothalamus and induce them to produce the biologically active substance prostaglandin E_2 (PGE_2). PGE_2 subsequently binds to its receptors on cells in the thermoregulatory center of the hypothalamus and induces reactions in neurons involving cyclic adenosine monophosphate (cAMP, a signaling molecule) and neurotransmitters to elevate the temperature set point.[135] Alternatively, it is also known that the proinflammatory cytokines interact with the endothelial cells lining the blood vessels of the hypothalamus and induce these cells to produce PGE_2, which can apparently cross the blood-brain barrier into the anterior hypothalamus. There is also indication that cytokines are actively transported through specific carriers across the blood-brain barrier. A further possibility in overcoming this barrier lies in the findings that afferent nerve fibers of the vagus nerve may transport inflammatory cytokines to the thermoregulatory centers of the hypothalamus.[136] In addition, there is evidence that the blood-brain barrier becomes more penetrable with an increasing immune response, and that activated T cells of the immune system can readily enter the brain parenchyma, whereas non-activated T cells are excluded under normal conditions.[137]

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131 Steinman, L.: Elaborate interactions between the immune and nervous systems. In: Nature Immunology 5 (2004), pp. 575-581.

132 Inui, A.: Cytokines and sickness behaviour: implications from knockout animal models. In: Trends in Immunology 22 (2001), pp. 469-473.

133 Petty, M.A./Lo, E.H.: Junctional complexes of the blood-brain barrier: permeability changes in neuroinflammation. In: Progress in Neurobiology 68 (2002), pp. 311-323.

134 Licinio, J./Frost, P.: The neuroimmune-endocrine axis: pathophysiological implications for the central nervous system cytokines and hypothalamus-pituitary-adrenal hormone dynamics. In: Brazilian Journal of Medical and Biological Research 33 (2000), pp. 1141-1148; Steinman (2004), op. cit.

135 Tsai, S.M. et al.: Pyrogens enhance β-endorphin release in hypothalamus and trigger fever that can be attenuated by buprenorphine. In: Journal of Pharmacological Science 93 (2003), pp. 155-162.

136 Licinio/Frost 2000, op. cit.; Steinman 2004, op. cit.

137 Boulanger, L.M./Shatz, C.J.: Immune signalling in neural development, synaptic plasticity and disease. In: Nature Reviews Neuroscience 5 (2004), pp. 521-531.

5.2.1 Malign Manipulation?

In the preceding section possible ways in which the immune system can regulate functions of the nervous system were briefly examined. Some of the consequences of using these regulatory elements with malign intent will now be discussed in more detail.

Proinflammatory cytokines can have several different effects on the nervous system. As may be recalled, these cytokines include IL-1β, TNFα and IL-6, all of which can apparently induce the state known as sickness behaviour, including fever, sleepiness, lethargy, loss of appetite and body weight loss. However, although IL-1β and TNFα do without a doubt contribute to the febrile response, the production of IL-6 is apparently crucial. This was seen in experiments with transgenic mice that were manipulated to overproduce a naturally occurring antagonist of the receptor for IL-1β (IL-1ra), which blocks IL-1β effects. Systemic injection of LPS still triggered a febrile response in these mice. Similarly, LPS could induce fever in mice lacking receptors for TNFα. However, neither LPS, IL-1β nor TNFα could induce fever in IL-6 deficient mice.[138]

Nevertheless, TNFα and IL-1β can be considered just as significant in mediating sickness behaviour, because TNFα can induce the production of both IL-1β and IL-6, while IL-1β can induce the production of IL-6.[139]

Another effect of IL-1β and the other proinflammatory cytokines on the central nervous system is the induction of the production of corticotropin-releasing factor (CRF) from the hypothalamus.[140] IL-1β is a major upregulator of CRF. In an earlier part of this chapter, it was discussed how CRF can lead to suppression of immune responses through its action on the pituitary to secrete ACTH, which in turns acts on the adrenal gland to induce the production of glucocorticoids. However, CRF has a profound effect on the nervous system as well. In this regard, overproduction of the hormone has been implicated with neurotoxicity and neurodegeneration in animal studies. In addition, CRF has been implicated with major depression, anorexia nervosa and Alzheimer’s disease.[141]

The immune system is involved in many illnesses associated with the nervous system, and one can see a clear division of these types of disorders, which are a reflection of the elements of immunity that are thought to be involved. Innate immune responses are associated with neurodegenerative diseases such as Alzheimer’s and Parkinson’s diseases, in which proinflammatory cytokines and complement components are present in the central nervous system. On the other hand, specific antibody and T lymphocyte responses (adaptive immune responses) to acetylcholine receptors are seen in myasthenia gravis, while antibody responses to the glutamate receptor, which cause the blockade of glutamate-mediated synaptic transmission, are apparent in Rasmussen encephalitis, resulting in epilepsy. The occurrence of these diseases with the involvement of various components of innate and adaptive immunity shows that such elements can indeed have devastating effects on the nervous system, when the delicate balance between activation and inhibition is broken.

When considering the possibility of using components of the immune system with malign intent, the question arrises as to the feasibility of targeting these elements to the central or autonomic nervous system. In its medical research work on endogenous bioregulators the

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138 Inui (2001), op. cit.

139 Abbas, A.K./Lichtman, A.H./Pober, J.S.: Cellular and Molecular Immunology. Philadelphia: W.B. Saunders Company 1997.

140 Straub, R.H./Westermann, J./Schölmerich, J./Falk, W.: Dialog between the CNS and the immune system in lymphoid organs. In: Immunology Today 19 (1998), pp. 409-413.

141 Licinio/Frost 2000, op. cit.

US Army has reported that IL-1 was effective in aerosol form in basic pulmonary absorption studies.[142] It therefore stands to reason that administration of IL-1β in aerosol form might indeed be an effective delivery system for inducing sickness behaviour in a population.

Another possibility to be considered is the delivery of a substance through a vector, such as a bacterium. Apparently the former Soviet Union in its offensive biological weapons programme experimented with the production of weapons designed to affect the central nervous system. One of the proteins studied was myelin basic protein (MBP), which is a substance used in the investigation of experimental autoimmune encephalomyelitis (EAE). Apparently soviet scientists were successful in transferring the gene encoding the MBP into *Yersinia pestis*, the causative agent of plague.[143] Presumably, upon infection with the bacterium, the gene would be activated, MBP would be produced and initiate an autoimmune immune response. This agent was thus conceived as a super weapon designed to cause two devastating diseases if it would work. What experiments were actually carried out was not reported.

A further possibility is to deliver the substance through a viral vector. Delivery of the cytokine IL-4 in the mousepox experiment by incorporating the gene into the mousepox virus was quite successful, albeit with a devastating outcome.[144] The possibility of manipulating a viral vector to gain neural tropism is not too far fetched, as discussed in Chapter 3. It should also be recalled that an ongoing immune response[145] and even stress itself can increase the permeability of the blood-brain barrier. [146]

Finally, aerosol delivery of peptides via the nasal route is being actively explored and seems to be promising in connection with drug delivery research. Nanotechnology combined with improved methods for absorption of substances across mucous membranes is making the delivery of peptide drugs much more feasible than in the past.[147] The nasal route is of particular interest because it can possibly provide direct access to the brain by entry into the olfactory bulb via axonal transport along nerve cells.[148]

5.3 Compounded Assault

We talk of the nervous system, the endocrine system and the immune system as if they were separate entities. This mode of analysis comes about because of the different pathways by which neuroscience, endocrinology and immunology have developed within the history of biology. In fact, of course, in the living organism these systems are thoroughly integrated in order that the animal (or human) functions in a unified way. Indeed, it is rather surprising that in recent years there has been so much surprise at the findings that demonstrate how closely the immune system is linked to the other two

142 USAMRIID: Basic studies seeking generic medical countermeasures against agents of biological origin. In: Annual Report for Fiscal Year 1987, p. 19.

143 Alibek, K./Handelman, S.: Biohazard. The Chilling True Story of the Largest Biological Weapons Program in the World - Told from Inside by the Man Who Ran It. New York: Random House Inc. 1999.

144 Jackson et al. 2001, op.cit.

145 Boulanger/Shatz 2004, op. cit.

146 Esposito, P. et al.: Acute stress increases permeability of the blood-brain barrier through activation of brain mast cells. In: Brain Research 888 (2001), pp. 117-127.

147 Davis, S.S./Illum, L.: Absorption enhancers for nasal drug delivery. In: Clinical Pharmacokinetics 42 (2003), pp. 1107-1128.

148 Graff, C.L./Pollack, G.M.: 2005 Nasal drug administration: potential for targeted central nervous system delivery. In: Journal of Pharmaceutical Sciences 94 (2005), pp. 1187-1195.

systems. There is a fine network of checks and balances exerted on the operation of all three systems by the elements within each of them. The perturbation of the function of one system will invariably have profound effects on the operation of the others. All three systems are interconnected through the hypothalamus-pituitary-adrenal axis via cytokines, hormones, neurotransmitters, peptides and their receptors, and also through innervation of neural and lymphoid organs and even cells of the immune system themselves.

Here then is an ideal target for those with malign intent. Clearly, if the complex balancing feedback system briefly illustrated in this chapter could be disrupted by the use of a bioregulator, an ideal method of incapacitation would be available to the attacker. From the point of view of potential malign manipulation, it follows that there is necessarily a new level of complexity. If malign manipulation of one system can affect two or three systems the defender's problem of diagnosis and treatment increases out of all proportion to the attacker's effort.

6 Assessing the Adequacy of the CBW Prohibition Regimes for the Challenges of the 21st Century

Multilateral prohibition regimes are more than the legal texts on which they are based. In addition to this legal dimension, the concept of “international regimes” captures the political dimension of states acting on their own (at the domestic level) and interacting with one another (at the international level) in the implementation of these legal arrangements. As states participate in international regimes of their own free will, there is an expectation that they will try to comply with the stipulations of the regime. In addition, as these regimes are often created to overcome collective action problems, participating states can be expected to have an interest in adapting a regime when the character of the underlying problem changes.

Certainly the bar for what qualifies as “best practice” in setting up arms control regimes is much higher today. This best practice standard finds its expression in a number of features of the regime like the availability of verification measures, or alternatively, procedures to provide transparency, the strength of the norms that are guiding state action, the provision of sanctioning mechanisms, the universality of the control measures agreed upon, and the adaptability of the regime structure to changing circumstances.

Although all of these features impact on the effectiveness and robustness of the CBW prohibition regimes, it is the last of the above characteristics, i.e., the regime’s capacity to adapt to S&T change, which we are especially interested in. We therefore first summarize the current revolution in the life sciences, thus broadening again our discussion of the selected areas presented in the preceding three chapters. This will be contrasted with the evolution of the two prohibition regimes which takes place in slow motion.

6.1 Life Sciences on the Fast Track

6.1.1 The Biotechnology Revolution

It was not until the advent of the “Golden Age” of bacteriology at the end of the 19th century that a scientific understanding of the nature of infectious diseases began to be acquired.[149] The fundamental mechanism of evolution was elucidated by Charles Darwin some one hundred and fifty years ago. It took another one hundred years before the structure of the hereditary material -DNA - was deciphered by Watson and Crick and another fifty years for the structure of the human genome to be described. Now discoveries at the core of biology are coming thick and fast. A look at what has followed from the Human Genome Project can give a clue as to how the biotechnology revolution might evolve.

As an example, new methods for DNA synthesis (e.g. on microchips) as well as new methods of error correction will reduce the cost and time for synthesizing long stretches of DNA. These capabilities will allow biologists to investigate more effectively many critical processes, but they will also, for example, increase the ability to synthesize new viral

149 Dando, M.R./Nathanson, V./Darvell, M.: Biotechnology, Weapons and Humanity. London: Harwood Academic Publishers 1999.

pathogens. Some of the people involved in this work have recognized the dangers and suggested the need for better controls.[150]

Other techniques related to the manipulation of DNA are also advancing rapidly. These include, for example the technique of DNA shuffling (the breaking up of DNA sequences and recombination of the fragments into many related versions), and the technique of RNAi (RNA interference), which is emerging as the most potent, effective and practical method of interfering with or silencing the expression of a specific target gene.[151]

Another emerging technology that is “on the threshold of synthesizing new life forms” [152] is that of synthetic biology, which is the design and assemblage of interacting genes into circuits in order to direct cells to perform new tasks. The aim is to be able to develop artificial models of how circuits work in nature and then to test out the predictions from the models in circuits that have been built in living tissues.[153] This technology is one of the most difficult to master and requires concerted effort from different disciplines such as engineering, computer science and biology.[154] Nevertheless, surprisingly rapid progress can be made in seemingly complex problems. Indeed, it has “opened up extraordinary possibilities for biomedical discovery and environmental engineering”, but at the same time the “scope for abuse or inadvertent disaster could be huge”.[155]

The relative new area of systems biology looks at interacting physiological systems and seeks to understand how all the parts of the body operate as a whole. It is “an emerging field that is characterized by the application of quantitative theoretical methods and the tendency to take a global view of problems in biology.”[156] It is not just that systems biology offers a promise of a genuinely mechanistic biology which is at the root of this change. There are very sound applied technological reasons for the approach to be supported by industry. We should expect pharmaceutical companies interested in drug discovery to encourage the growth of systems biology.

By standing back a little from our direct concerns with bioterrorism and biowarfare we can also see the value of George Poste’s famous exhortation[157] to his colleagues to think well “beyond bugs”. Thus, the genomics revolution allowed the structure of many proteinaceous cellular receptors to be elucidated, but now that knowledge enables us to more rapidly investigate how neuronal and other circuits function (systems biology). There is presently a real feeling of accelerating discoveries across many areas of biology as well as at the core.

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150 Church, G.: A Synthetic Biohazard Non-Proliferation Project 2004, available at: <http://arep.med.harvard.edu>.
151 Sandy, P./Ventura, A./Jacks, T.: Mammalian RNAi: a practical guide. In: BioTechniques 39 (2005), pp.215-224.
152 Ball, P.: Starting from scratch. In: Nature 431 (2004), pp. 624-626.
153 Garcia-Ojalvo, J. et al.: Modelling a synthetic multicellular clock : Repressilators coupled by quorum sensing. In: Proceedings of the National Academy of Sciences USA 101 (2004), pp.10955-60.
154 Check, E.: Designs on life. In: Nature 438 (2005), pp 417-418.
155 Ball 2004, op. cit.
156 Goldbeter, A.: Computational biology: a propagating wave of interest. In: Current Biology 14 (2004), pp. R601-R602.
157 Poste, G.: Advances in biotechnology: promise or peril. Available at: <www.hopkins-defense.org/sympcast/ transcripts.trans_poste.html>.

6.2 Prohibition Regimes Evolving in Slow Motion: Undermining Regime Adequacy?

6.2.1 The BW Prohibition Regime

As noted at the beginning of this chapter, there is more to international regimes than the treaties they are often based on. In the case of the BW prohibition regime which does not have at its disposal an international organization to oversee implementation of the regime's standards for behaviour, the five-yearly Review Conferences assume critical importance in this regard. These Conferences offer an important opportunity to take stock of treaty implementation, and the final declarations provide useful clues for the shared interpretations of regime members on the status of regime adequacy.

In chapter 2 we have made the point that successive review conferences have found the possible misuse of S&T advances in the life sciences to be covered by the scope of the BWC. What has changed dramatically over time, however, is the assessment of the misuse potential of new scientific developments. For the First Review Conference the three Depositary States – United Kingdom, United States of America and the then Soviet Union - produced a joint paper on relevant scientific and technical developments.[158] The assessments made in the paper appear today to have been somewhat optimistic. In regard to the new recombinant DNA techniques, for example, the paper states that:

> "Although recombinant DNA techniques could facilitate genetic manipulation of micro-organisms for biological or toxin warfare purposes, the resulting agents are unlikely to have advantages over known agents sufficient to provide compelling new motives for illegal production or military use in the foreseeable future [...]"[159]

How many of us would agree with such sentiments today?

For the Third Review Conference in 1991 a number of States Parties (Australia, Czechoslovakia, Sweden, the UK and the USA) produced contributions for the background paper on scientific and technological developments.[160] The UK contribution is particularly useful for our purposes since it used the same sections as the 1980 paper by the Depositary States. It therefore offers the possibility of directly comparing the conclusions.

For recombinant DNA techniques, now termed genetic modification (GM), the UK concluded that:

> "[...] There has been steady refinement of those biotechnology aspects other than GM that an aggressor nation could misuse in developing an offensive BW capability; important among the capabilities that could be misused are techniques

158 United Nations. Depository States: New Scientific and Technical Developments Relevant to The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. Document BWC/CONF.I/5. Geneva: United Nations, 6 February 1980. Available at <http://www.opbw.org>.

159 Ibid, p. 8.

160 United Nations. Background Paper: New Scientific and Technical Developments Relevant to The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. Document BWC/CONF.III/4. Geneva: United Nations, 26 August 1991. Available at <http://www.opbw.org>.

for the large-scale production of natural or modified micro-organisms or toxins [...]"[161]

and it noted that further advances in such capabilities were to be expected.

As should be expected, the general conclusion had also changed. While stressing that the BWC still covered all these developments and that some also had the potential to assist the defence, there is no doubting the changed view:

> "The current UK view is that worldwide the increase in knowledge of many of the pathogenic species of micro-organisms, and the knowledge of toxins and other biological agents, and the continuing pace of developments in civil biotechnology areas, have further increased the possibilities for production and hostile use of biological agents, whether naturally occurring or not."[162]

So the situation had progressively worsened over successive five-year periods. This general point was also made in the contributions by Australia and Sweden.

The changing scope of developments was further emphasised by the Canadians who produced a special monograph, "Novel Toxins and Bioregulators: The Emerging Scientific and Technological Issues Relating to Verification and the Biological and Toxin Weapons Convention". This monograph was circulated to all States Parties at the Review Conference. The issue of peptide bioregulators was also covered in some detail by the United States:

> "Their range of activity covers the entire living system, from mental processes (e.g. endorphins) to many aspects of health such as control of mood, consciousness, temperature control, sleep, or emotions, exerting regulatory effects on the body. Even a small imbalance in the natural substances could have serious consequences, including fear, fatigue, depression or incapacitation."[163]

In general, the United States agreed that "the confidence derived from the belief that certain technical problems would make biological weapons unattractive for the foreseeable future has eroded".[164]

There is no doubt that there had been a major change in the perceptions of the contributors to these background papers between 1980 and 1991. However, the situation regarding review and agreed final statements deteriorated significantly thereafter. Although the disruption caused by the United States at the 2001 Review Conference prevented a final declaration from being made, it is nevertheless possible to examine the background paper on S&T changes produced by States Parties and to compare the 2001 versions with that of 1991.

The background paper for the 2001 Review Conference had contributions from Bulgaria, South Africa, Sweden and the United States[165] and by the UK[166]. The South African

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161 Ibid, P.22.

162 United Nations. Background Paper: New Scientific and Technical Developments Relevant to The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Theirs Destruction. Document BWC/CONF.III/4. Geneva: United Nations, 26. August 1991. Available at <http://www.opbw.org>.

163 Ibid, p. 29.

164 Ibid, p. 33.

165 United Nations. Background Paper: New Scientific and Technical Developments Relevant to The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on

contribution began by noting that there were many developments relevant to the Convention, but signalled its intention to deal just with biocontrol agents and plant inoculants, which is significant because anti-plant biological warfare possibilities are frequently neglected. The contribution of Sweden referred to the well-known inadvertent outcome of the Australian mousepox experiment and pointedly suggested that it showed that even inadvertent outcomes of peaceful research could "play into the hands of those with malevolent aims."

The UK states that "Given the accelerating pace in science and technology, the UK wonders whether it is prudent to maintain a five-year gap between such assessments under the BTWC."

Significantly, the UK text continued with a specific practical proposal:

> "[...]The UK suggests that the upcoming Review Conference consider establishing a mechanism for State Parties to work together on a more frequent basis to conduct such scientific and technical reviews and to consider any implications at the necessary level of expertise."[167]

Unfortunately, it would appear that this idea of designing a more adequate collective means of assessing and responding to scientific and technological change was lost amongst so much else in the chaos of the 2001-2002 Review Conference.

The events of September 2001 in the US significantly changed many people's appreciation of the dangers, and new concerns began to be raised in public. However, it is questionable whether these new concerns have been translated into an overall strengthening of the BW prohibition regime. On the multilateral level the Inter-Review Conference process has focused on a small number of selected issue areas, and although a substantial amount of information has been provided by the States Parties, much is related to national implementation of the BWC. This issue should have been addressed three decades ago. So at best the current exercise represents an attempt to catch up with BWC implementation as it is required under the Convention.

Not only has the US been instrumental in bringing the work of the Ad Hoc Group to an end, it has also increased dramatically biodefence activities.[168] If one considers biodefence and BW arms control to represent two sides of the same coin in the battle against BW, this clearly represents a shift in priorities away from the multilateral enterprise of regime building and strengthening towards an increased reliance on national preparedness.

Their Destruction. Document BWC/CONF.V/4. Geneva: United Nations 14 September 2001. Available at <http://www.opbc.org>.

166 United Nations. Background Paper: New Scientific and Technical Developments Relevant to The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. Document BWC/CONF.4/Add.1. Geneva: United Nations 26 October 2001. Available at <http://www.opbc.org>.

167 Background Paper: New Scientific and Technical Developments Relevant to The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. Document BWC/CONF.4/Add.1. Geneva: United Nations 26 October 2001, p. 6. Available at <http://www.opbw.org>.

168 Kelle, A.: Bioterrorism and the Securitization of Public Health in the United States of America – Implications for Public Health and Biological Weapons Arms Control. In: Bradford Regime Review Paper No. 2. Bradford: University of Bradford (July 2005), p. 2. available at: <http://www.brad.ac.uk/acad/sbtwc/regrev/Kelle_SecuritizationinUS.pdf>.

6.2.2 The CW Prohibition Regime

Since the CWC's entry into force in 1997 CW stockpiles in the declared possessor states are being destroyed under international verification and no instances of proliferation among CWC States Parties or with their help have been recorded. Thus, taking a narrow interpretation of the regime's purpose, there seems to be no need to worry about the regime's adequacy.

Proponents of a second view would point to the CWC drafters' awareness of the fact that the CW prohibition regime has to operate in a dynamic scientific and technological environment. In this regard, the CWC contains tools to make its States Parties aware of S&T change – in the form of a scientific advisory board (SAB) – and to address this change, either collaboratively between the OPCW's Technical Secretariat and member states or during a regular Review Conference. However, the portfolio of the SAB seems to be rather limited and the only full-scale assessment of S&T advances of relevance to the CWC was undertaken prior to the first CWC Review Conference. If this exercise is repeated for the next Review Conference, the CW prohibition regime will fall into the same five-yearly pattern of assessing S&T advances that BWC States Parties have displayed in the past. One exception to this pattern was mentioned in Chapter 2 and because of its significance it is worth repeating here. The SAB report submitted to the Director General pointed out that it was concerned about the development of new riot control agents (RCAs) and other so-called "non-lethal" weapons; the science related to such agents was developing rapidly and programmes to develop such agents should be closely monitored and assessed according to their relevance to the Convention.[169]

Our own research confirms the SAB's assessment that advances in neuroscience underlying toxic incapacitants is evolving rapidly. Unfortunately, the SAB's call for monitoring and assessing these programmes up to now seems to have fallen on dead ears on part of the CWC's States Parties. Should this attitude on the part of some influential States Parties prevail, it does not bode well for the prospects of the CW control regime to be kept up to date and thus be adequate to deal with the challenges ahead.

169 Note by the Director General: Report of the Scientific Advisory Board on Developments in Science and Technology. OPCW Document RC-1/DG.2. The Hague: 23 April 2003, p.15.

7 Conclusion: Towards an Overarching Framework for Biochemical Controls

The evidence from the life science laboratories is quite clear: there is going to be an increasing risk that new discoveries will facilitate both state-level offensive biological weapons programmes and sub-state (terrorist) development of biological weapons. For over a decade it has been clear that only a wide-ranging integrated web of policies will be adequate to prevent this misuse of our new scientific and technological capabilities taking place. The web of deterrence[170] or web of prevention consists, at the very least, of:

> “comprehensive, verifiable, global CB arms control to create a risk of detection and a climate of political unacceptability for CB weapons;
> broad export monitoring and controls to make it difficult and expensive for a proliferator to obtain necessary materials;
> effective CB defensive and protective measures to reduce the military utility of CB weapons; and
> a range of determined and effective national and international responses to CB acquisition and/or use.”[171]

Thus, the proposed web of prevention encompasses the two CBW prohibition regimes, but goes beyond them in that it includes additional defensive, counterproliferation, and supply-side measures like export controls and the interdiction of shipments that might contribute to CBW proliferation. What it does not account for, however, is the paradigm shift we outlined in chapter 1 and which has guided the selection of the areas of S&T advances we have focused our attention on: the shift from CBW agents and possibilities of their manipulation towards the malign manipulation of selected physiological targets in the human body. In light of this paradigm shift it might no longer suffice to make all elements of the web as strong as possible, to persuade any proliferator contemplating the development of chemical or biological weapons that it is more likely that the potential costs far outweigh any benefits.

The question thus becomes how to achieve the appropriate strengthening of the various policy elements in the web and how to devise an overarching framework that would tie together all the measures that have been proposed and that will be needed additionally to account for the paradigm shift allowing future biochemical warfare. Given the slow and difficult progress of recent years it is safe to assume that no quick fixes will be available. Rather, a slow and iterative process of adapting and expanding existing prohibitions and controls both at the national and international level will be required.

170 Pearson, G.S.: Prospects for chemical and biological arms control: The web of deterrence. In: The Washington Quarterly 16 (1993), pp. 145-162.
171 Dando et. al. 1999, op.cit.

7.1 National Measures

Both the CWC and BWC have the requirement that necessary national measures are enacted to implement the treaties within States Parties, but the implementation of this requirement has been unsatisfactory for both agreements. With its organisation and regular meetings the situation in regard to the CWC is beginning to be rectified through the operation of a specific action plan.[172] Investigation revealed that the reasons for failure to implement the national legislative requirement were frequently administrative or bureaucratic, not political, so appropriate assistance could greatly assist in effective rectification of the deficiency. The BWC has neither an organisation nor regular meetings, so development and implementation of such an action plan are far less likely. It may be that implementation of Security Council Resolution 1540 (to be discussed under international measures below) will have some effect on BWC national implementation, but this cannot be guaranteed.

Considering the importance of implementation it was perfectly appropriate for the first (2003) meetings of the Inter-Review Conference process to consider:

> "i) the adoption of necessary national measures to implement the prohibitions set forth in the Convention including the enactment of penal legislation."[173]

The problem, of course, is that the Inter-Review Conference process had a mandate only to "discuss and promote common understanding and effective action" on the topics under consideration.[174] Only at the Sixth Review Conference will the States Parties "consider the work of these meetings and decide on any further action."

Given the increasing concern over misuse of the life sciences by sub-state actors since the initial formulation of the idea of a web of deterrence in the early 1990s, the second topic for discussion at the 2003 meetings was also understandable. This was consideration of:

> "ii) national mechanisms to establish and maintain the security and oversight of pathogenic microorganisms and toxins." [175]

No doubt, in a number of countries such as the UK, considerable efforts have been and are being made to achieve such goals.[176] But the fact remains that consideration of concerted international action will only be decided at the 2006 Sixth Review Conference of the BWC.

In considering disease monitoring it was recognised *inter alia* that "strengthening and broadening national and international surveillance, detection, diagnosis and combating of

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172 Spence, S.: Achieving Effective Action on Universality and National Implementation: the CWC Experience. Briefing Paper No. 13. Bradford: University of Bradford April 2005.

173 United Nations: Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction: Report of the Meeting of States Parties. Document BWC/MSP/2003/4 (Vol.I). Geneva: United Nations 26 November 2003.

174 Ibid.

175 Ibid.

176 Pearson, G.S.: Security and oversight of pathogenic microorganisms and toxins. In: Chemical and Biological Weapons Conventions Bulletin 60 (2003), pp. 6-15.

infectious disease may support the objective and purpose of the Convention" [177], and that "the primary responsibility for surveillance, detection, diagnosis and combating of infectious diseases rests with States Parties".

Regarding capabilities for responding to cases of alleged use of biological weapons, they also recognised that "States Parties' national preparedness and arrangements substantially contribute to international capabilities for responding to, investigating and mitigating the effects of cases of alleged use of biological or toxin weapons or suspicious outbreaks of disease."

However, in a step forward from the 2003 meeting of States Parties, the 2004 report also stated that "State Parties are encouraged to inform the Sixth Review Conference of, *inter alia*, any actions, measures, or other steps that they may have taken on the basis of the [2004] discussions."[178] This will again clearly facilitate the process of strengthening of regime implementation at the national level.

7.1.1 Codes of Conduct for Life Scientists

In 2005 the Inter-Review Conference process turned to the very different topic of "the content, promulgation, and adoption of codes of conduct for scientists".[179] This clearly raised issues which were well outside the usual range of discussions at BWC meetings, brought in a new constituency of interest - life scientists - and brought much more clearly into focus the impact of the ongoing scientific and technological revolution.

Fortunately, the complexities of the subject of codes of conduct were clarified at the meeting and as one detailed report noted "there appears to be recognition of the value of a matrix of code".[180] These codes would be composed of:

> "[...] an overarching set of moral and ethical principles which might have wide applicability, a code of conduct which could give guidance and, at the more detailed level, an extension to an existing national code of practice which might set out steps that need to be taken as a regular process when any new work is being considered [...]". [181]

Unfortunately, it also became clear from many sources that life scientists had little awareness of the problem of the dual uses - benign or malign - to which their work might be applied.[182] Thus, to make any progress on the development of codes of conduct within the various States Parties to the BWC a major awareness-raising programme will have to be undertaken.

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177 United Nations: Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction: Report of the Meeting of States Parties. Document BWC/MSP/2004/3. Geneva: United Nations 14 December 2004.

178 Ibid.

179 United Nations: Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction: Report of the Meeting of States Parties. Document BWC/MSP/2005/MX/3. Geneva: United Nations 5 August 2005.

180 Pearson, G.S.: Report from Geneva No. 23: The Biological Weapons Convention Meeting of Experts. In: The Chemical and Biological Weapons Conventions Bulletin 68 (2005), pp.12-19.

181 Ibid.

182 Dando, M.R./Rappert, B.: Codes of Conduct for the Life Sciences: Some Insights from UK Academia. Briefing Paper No. 16. Bradford: University of Bradford May 2005.

7.1.2. Oversight of Research

In one country at least this awareness-raising is beginning in earnest. As previously noted, the United States National Academies, in response to growing concerns about the misuse of modern biology, set up a committee under the chairmanship of Gerald Fink to examine the issues involved. The committee report, "Biotechnology Research in an Age of Terrorism: Confronting the Dual-Use Dilemma",[183] in part identified seven classes of experiments that it felt required prior review. The classes were those which:

> "- would demonstrate how to render a vaccine ineffective;
> - would confer resistance to therapeutically useful antibiotics or antiviral agents;
> - would enhance the virulence of a pathogen or render a nonpathogen virulent;
> - would increase transmissibility of a pathogen;
> - would alter the host range of a pathogen;
> - would enable the evasion of diagnostic/detection modalities; and
> - would enable weaponisation of a biological agent or toxin."[184]

The report favoured a voluntary scheme of self-regulation, but suggested that a national board be set up to oversee and develop the scheme. The US government accepted this idea and moved to found a National Science Advisory Board on Biosecurity (NSABB). The NSABB held its inaugural public meeting in Washington D.C. in mid-2005 and detailed explanations of what had been done were given to the BWC meeting of experts in Geneva.

In chapter 2 we have pointed out that in response to worries about scientific publications like that on the mousepox experiment, the editors of a number of major scientific journals had agreed on a system of checking submitted papers for possible inadvertent assistance being given to terrorists. However, this had resulted in very, very few papers even being questioned, let alone modified or refused publication. In light of the questionable value of self-regulatory efforts by scientific publishers, the NSABB model was regarded by many as an important potential model for other states' national oversight systems in the future. The difficulties with the proposed system, however, should not be underestimated.

What was being proposed as oversight by the Fink Committee appeared to be a tiered review system in which experiments in the designated classes would be subject to local review and then, if there were difficulties at that level, the national system would become involved. A group at the University of Maryland, which had given considerable attention to such a tiered review system, has expressed a number of concerns. They suggested that the system had to cover all institutions involved in biotechnology research (including civil industry and biodefence), that it had to be based on law, not guidelines, and that an effective system needed to be international, not just national.[185]

Biodefence is a particular concern.[186] Legitimate biodefence is permitted under the BWC and needs to be appropriately strengthened as part of the overall web of prevention against the hostile use of modern biology. But biodefence is necessarily going to be carried out in areas of research which are related to offensive possibilities. Certainly, there has been a huge increase in biodefence funding in the United States, including that for the

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183 NAS Committee on Research Standards and Practices to Prevent the Destructive Application of Biology. Biotechnology Research in an Age of Terrorism: Confronting the Dual-Use Dilemma. Washington, DC: The National Academies Press 2003.

184 Ibid.

185 Steinbruner, J.D./Harris, E.D.: Controlling dangerous pathogens. In: Issues in Science and Technology 19 (2003). Available at <http://www.issues.org/issues/19.3/steinbruner.htm>.

186 Dando, M.R./Wheelis, M.L.: Back to bioweapons? In: Bulletin of the Atomic Scientists 59 (2003) pp. 40-46.

National Institutes of Health which grew “by over 3,200%, from $53 million in fiscal year 2001 to a record $1.8 billion (requested) in fiscal year 2006”.[187] Such increases are always likely to raise questions.

It is generally agreed that the community of practising chemists and their professional societies played an important positive role in the negotiation of the Chemical Weapons Convention. This positive role has continued, with the International Union of Pure and Applied Chemistry (IUPAC) making a major contribution on scientific developments for the 2003 First Review Conference of the CWC. More recently, IUPAC had joined with the OPCW in its efforts to develop new educational aids to inform the profession of the importance of the CWC.

The BWC obviously lacks an organisation like the OPCW, but what is less well known is that the disparate international professional societies of biologists lack an overarching organisation like IUPAC. Getting an international assessment from the world's biologists of present and future developments and what might best be done is therefore very difficult. The UK Royal Society has argued that there is a need for the BWC to have a Scientific Advisory Panel to carry out such assessments.[188] This is a sensible idea but, in view of the difficulties in agreeing anything to strengthen the BWC,[189] it might be that the individual national academies will have to pursue this idea as a co-operative venture outside of the Convention until the prospects for the international regime improve.

7.2 Adapting CBW Controls on the International Level

As outlined in previous chapters attempts to strengthen the BW prohibition regime through the negotiation of a legally binding compliance protocol and to adapt the CW prohibition regime to changes in chemical industry and S&T advances have either been a complete failure – in the case of the AHG work on a BWC Compliance Protocol – or seen rather limited success – in the CW realm. The new Inter-Review Conference process established by the last BWC Review Conference in 2001/2002 focussed more on national implementation measures in the selected areas that were being covered than genuinely moving the regime forward.

However, there have been a few initiatives of an international character that have supplemented the two prohibition regimes in the areas of export controls and interdiction of NBC-related materials. Two of these will be discussed in the following section. This will be followed by a discussion of some proposals that have been made for strengthening the regimes through the negotiation of a biosecurity convention, the criminalization of CBW and the setting up of a small organisational infrastructure in support of the BWC. Yet, as all these proposals fall short of offering a coherent framework in which either their relationship to the CBW prohibition regimes is somewhat unclear, or they do not aim to integrate the various measures in existence and being proposed, or they do not take into account the paradigm shift with which we are concerned, we propose negotiation of a Framework Convention on Biochemical Controls (FCBC), a provisional outline of which will be presented in the final section of this chapter.

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187 Harris, E.D./Steinbruner, J.D.: Scientific openness and national security. In: Chemical and Biological Weapons Conventions Bulletin 67 (2005), pp. 1-6.

188 Royal Society: Royal Society Submission to the Foreign and Commonwealth Office Green Paper on Strengthening the Biological and Toxin Weapons Convention. Policy Document 25/02. London: Royal Society 2002.

189 Ward, K.D.: The BWC Protocol: Mandate for Failure. In: The Nonproliferation Review 11 (2004), pp.183-99.

7.2.1. Measures Already Adopted

The Proliferation Security Initiative (PSI) was initiated by the US administration under President Bush in May 2003. It establishes a framework for "multinational response to the growing challenge posed by the proliferation of weapons of mass destruction (WMD), their delivery systems, and related materials worldwide." [190]

The Initiative started with 11 founding members and has so far attracted support from more than 60 additional states. In early 2004 the US signed two Ship Boarding Agreements with Liberia and Panama, respectively. This represents a significant step towards universalization of the PSI principles as roughly "50% of the world's shipping volume is carried on flag vessels of the core PSI participants, as well as Panama, and Liberia."[191] Since then similar agreements have been signed with the Marshall Islands (August 2004), Croatia (June 2005), Cyprus (July 2005) and Belize (August 2005).

PSI participants have emphasized the compatibility of the initiative with the two CW and BW prohibition regimes. However, as one recent interpretation of PSI as a building block of an "increasingly decentralized nonproliferation architecture"[192] shows, it represents only a partial solution to the wider biochemical threat we are facing: it focuses exclusively on one part of the supply side of the proliferation problem – as it does not address intangible technology transfers – and does not take into consideration the paradigm shift away from pathogens or toxic chemicals as weapons and towards the physiological targets in the human body.

UN Security Council Resolution 1540 of 28 April 2004[193] addresses some of the limitations inherent in the PSI-approach, as first of all the export control measures required under it are not excluding intangible technology transfers. It also has a much wider scope than PSI prohibiting state support for non-state efforts to acquire NBC weapons, requiring states to:

> "adopt and enforce appropriate effective laws which prohibit any Non-State actor to manufacture, acquire, possess, develop, transport, transfer or use nuclear, chemical or biological weapons and their means of delivery".[194]

Resolution 1540 furthermore requires all states to undertake "appropriate effective measures to account for", "effective physical protection measures" and "appropriate effective border controls and law enforcement efforts" in order to secure NBC-weapons and related material and prevent their misuse by non-state actors. In addition it calls for "appropriate effective national export and trans-shipment controls" and sets up a Committee of the Security Council to examine states' reports on the status of their implementation of Resolution 1540.

For states already participating in the CW and BW prohibition regimes this is largely a reiteration and specification of commitments already undertaken under the BWC and CWC. However, the wording in Resolution 1540 makes these stipulations binding on all states, including those outside the prohibition regimes and in that sense presents a useful step forward in ensuring universality of the norms against CBW. Yet, the wording of the

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190 US Department of State, Bureau of Public Affairs: Proliferation Security Initiative. Washington, DC: 15 September 2003. Available at <http://www.state.gov/documents/organization/24252.pdf>.

191 Lehrman, T.D.: Rethinking interdiction: the future of the proliferation security initiative. In: The Nonproliferation Review 11 (2004), pp.1-45.

192 Ibid, p. 27.

193 United Nations: United Nations Security Council Resolution 1540. Adopted by the Security Council at its 4956th Meeting, on 28 April 2004, available at <http://disarmament2.un.org/Committee1540/Res1540(E).pdf>.

194 Idem.

resolution on the other hand also allows for loopholes in implementation. As it is not specified what constitutes “effective appropriate” action, states might simply report back to the Security Council Committee set up under the resolution that they are already taking such action. Furthermore, the time limitation of the Committee’s activities to two years presents an additional limitation on the positive effect the resolution might have. Especially when viewed from the perspective of S&T changes in the life sciences, a permanent institutional structure to examine states’ control efforts would be much more appropriate to monitor and react to the changing threat spectrum.[195]

7.2.2 Additional Measures Proposed

A number of additional measures have been proposed by academics and NGOs to strengthen or supplement the CW and BW prohibition regimes. One proposal advocates the establishment of international biosecurity standards.[196] Like the work by the Maryland University group of scholars mentioned above, Tucker focuses on preventive measures that could be taken to better secure pathogens that could be misused by terrorists for a BW attack. He correctly points out the absence of

> “uniform global standards for laboratory security […] on which individual states can base national legislation and regulations. This lack of harmonization, […], has given rise to gaps and vulnerabilities that must be addressed as part of a coordinated global strategy to prevent bioterrorism.”[197]

Elements of that strategy should include proper accounting mechanisms for pathogens and toxins, the registration and licensing of facilities handling pathogens and toxins, the establishment of physical security measures, and the screening of laboratory personnel.[198] Although UNSC Resolution 1540 seems to go a long way towards meeting these demands, the proposal put forward by Tucker contains much more detail in terms of the measures to be taken, aims at the harmonization of national measures, and provides for the establishment of an oversight mechanism which incorporates a small secretariat, both of which go well beyond the mandate of the 1540 Committee. Thus, agreement on more stringent international biosecurity standards along the lines proposed by Tucker could well serve as the next stage in the Security Council’s dealing with the bioterrorist threat in general and the oversight of pathogenic micro organisms and toxins in particular. Clearly, the Security Council would not be the right venue to negotiate such a treaty on global biosecurity standards, but its initiation and support of a negotiation process leading to such a legally binding instrument could be expected to create a positive momentum for negotiations in the Sixth Committee of the UN General Assembly.

A different new international treaty which would make for a very useful addition to both BWC and CWC and thus improve regime adequacy is a “Convention to Prohibit Biological and Chemical Weapons under International Criminal Law”. Such a Draft Convention has

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195 A more detailed account of the negotiation, content and implications of UN Security Council Resolution 1540 can be found in Datan, M.: Security Council Resolution 1540: WMD and non-state trafficking. In: Disarmament Diplomacy 79 (2005), pp. 48-60; Craft, C.: Challenges of UNSCR 1540: Questions about International Export Controls. CITS Briefs. Athens: University of Georgia 2004.

196 Tucker, J.B.: Biosecurity: Limiting Terrorist Access to Deadly Pathogens. In: Peaceworks No.52. Washington, DC: United States Institute of Peace (November 2003), pp. 1-52.

197 Ibid, p.5.

198 Ibid, pp.29-34.

been formulated by the Harvard Sussex Program on CBW Armaments and Arms Limitation.[199] While both BWC and CWC require states parties to enact domestic legislation which criminalizes the prohibitions contained in these treaties, the new convention would put acts involving biological and chemical weapons on an equal footing with aircraft hijacking or torture. As pointed out by the authors of the draft convention, "[p]urely national statutes present daunting problems of harmonizing their various provisions regarding the definition of crimes, rights of the accused, dispute resolution, judicial assistance and other important matters."[200]

At its core under the proposed convention:

> "[e]ach State Party would be required, inter alia, (i) to establish jurisdiction with respect to such crimes according to established principles of judicial law, including the principles of territoriality, nationality, protection, and passive personality, and (ii) where the state has jurisdiction and if satisfied that the facts so warrant, to submit those cases to competent authorities for the purposes of extradition or prosecution. Further with respect to actual use of biological and chemical weapons, each State Party would be required to establish jurisdiction over all persons found on its territory regardless of their nationality or place of the offence."[201]

While such new international treaties would enhance regime adequacy by increasing the norm and rule density in the issue area and thus complement BWC and CWC, other proposals are more closely linked to the BWC and have for example explored opportunities to address the "institutional deficit" of the BWC.[202] This would aim at improving the organizational capacities for better implementing already existing normative guideposts of the BW prohibition regime. Starting from the assumption that even after the collapse of the Ad hoc Group negotiations on a comprehensive organisational structure like the proposed Organisation for the Prohibition of Biological Weapons would represent the ideal solution for the BW regime's organisational deficit, Sims argues that

> "for the years immediately following the Sixth Review Conference some less ambitious proposals must suffice. These might comprise an annual meeting of States Parties, or an open-ended meeting of their Bureau, supported by a Scientific Advisory Panel and a permanent Secretariat. All would derive their authority from the Sixth Review Conference."[203]

This latter point is important as it makes clear that any such modest organisational setup would not require an amendment to the BWC, involving ratification by states parties. Sims builds a well-argued case in support of his proposal, quoting increasing support from BWC states parties during the past few years and also pointing to the nuclear non-proliferation treaty (NPT), where states parties have made similar proposals for establishing a mechanism for more regular reviews of the treaty than the five-yearly review conferences permit. However, as in the case of the NPT, it is not unrealistic to expect resistance on part of some states parties to increase formal interactions among BWC states parties between

199 See <http://www.sussex.ac.uk/Units/spru/hsp/CRIMpreambleFeb04.htm>.
200 Ibid.
201 See <http://www.sussex.ac.uk/Units/spru/hsp/CRIMpreambleFeb04.htm>.
202 Sims, N.A.: Remedies for the Institutional Deficit of the BTWC: Proposals for the Sixth Review Conference. Review Conference Paper No.12. Bradford: University of Bradford March 2005.
203 Ibid, p.4.

review conferences. Clearly the US government has made its unwillingness to engage in any such activities known.

7.3 Bridging the Gaps – Towards a Framework Convention for Biochemical Controls (FCBC)

As this brief discussion of a few of the already enacted or at least proposed measures to strengthen the BW and CW prohibition regimes clearly demonstrate, all of these initiatives and proposals are addressing only a part of the problems identified and practically none of them addresses in a meaningful way the paradigm shift in the life sciences we have explored in previous chapters and have illustrated by discussing advances in the neurosciences and in immunology. What is thus needed is an instrument to bridge the existing gaps and address the new challenges looming on the horizon of efforts to prevent the misuse of S&T advances in the life sciences.

We propose that such an instrument could take the form of a new Framework Convention on Biochemical Controls (FCBC). Framework conventions fall in the area of soft law which does not make legally-binding specific proscriptions for state action. They are a relatively new type of legal instrument which has been applied *inter alia* in the areas of international environmental and international health policy. The 1992 UN Framework Convention on Climate Change [204] and the 2003 WHO Framework Convention on Tobacco Control [205] are two examples of such conventions who aim at providing a wider framework for specific action to be agreed upon at a later stage. Given the lack of progress towards verification measures in the BWC context, it might be advisable to take a step back from the details of the two regimes and look at the larger picture of scientific and technological advances.

While a FCBC will not immediately address the structural shortcomings in the BW prohibition regime or improve compliance with the CWC's stipulations, its longer-term benefits would be considerable. They would be located in two areas: firstly, a FCBC could provide a bridge between issue areas that so far have been treated largely in isolation. This refers to both chemical and biological weapons developments, where an overlap in the subject matter, i.e. in regard to toxins, which is being regulated, is widely acknowledged, but where an overarching bracket is currently missing. While the separation of CW and BW made sense with respect to classical warfare agents and was useful in negotiating the BWC in the late 1960s and early 1970s, in the age of 21st century life sciences in which biological processes can be affected at the molecular level, the continued distinction will look increasingly out of touch with reality. The FCBC could also provide a stronger link between the prohibition of CBW and human rights. So far this link has been made only in relation to toxic incapacitants. Secondly, a FCBC could address the paradigm shift from the chemical or biological warfare agent as the object of malign manipulation to the physiological target in the human body, thereby contributing to the continued adequacy of the CBW prohibition regimes.

In order to provide these benefits the FCBC could be used as a vehicle by states to recognize the dual-use potential of biological and chemical agents and materials, equipment, technologies and know-how and to express their determination to prevent the misuse of chemical and biological agents and materials to incapacitate, kill or purposefully harm humans, animals, or plants. An FCBC would provide an opportunity to acknowledge

204 See <http://unfccc.int/2860.php>.
205 See <http://www.who.int/tobacco/framework/en/>.

the accelerating speed of scientific and technological advances in the life sciences and related scientific disciplines and also to acknowledge the above mentioned paradigm shift in the proliferation problem as knowledge that could be misused to target the human body is widely diffused. From this vantage point then, the framework convention should reflect the concern that an increased understanding of life processes at the molecular level will amplify the misuse potential of biological and chemical agents and materials, equipment, technologies and know-how to kill, harm, or otherwise incapacitate. The FCBC should make it clear that no person should be exposed to such biological and chemical materials without having given a prior informed consent to such exposure. States parties to the FCBC should be required to treat any violation of such a stipulation as a criminal act and make it punishable under national and international law. Last, but not least, the FCBC would have to be drawn up in a way that it does not contradict or detract from existing international treaties and other arrangements relating to chemical and biological agents and materials, most notably the CWC and BWC.

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Bibliography

Abbas, A.K./Lichtman, A.H./Pober, J.S.: Cellular and Molecular Immunology. 3rd Edition, Philadelphia: W.B. Saunders Company 1997.

Adams, G./Vessillier, S./Dreja, H./Chernajovsky, Y.: Targeting cytokines to inflammation sites. In: Nature Biotechnology 21 (2003), pp. 1314-1320.

Aftalion, F.: A History of the International Chemical Industry. From the “Early Days” to 2000 (2nd ed.). Philadelphia: Chemical Heritage Press, 2001, especially pp. 32-101.

Alcami, A./Koszinowski, U.H.: Viral mechanisms of immune evasion. In: Trends in Microbiology 8 (2000), pp. 410-418.

Alibek, K./Handelman, S.: Biohazard. The Chilling True Story of the Largest Biological Weapons Program in the World-Told from Inside by the Man Who Ran It. New York: Random House Inc. 1999.

Anderson, W.M.: Top ten list in sleep. In: Chest 122 (2002), pp. 1457-1460.

Aston-Jones, G. et al.: Role of locus coeruleus in attention and behavioural flexibility. In: Biological Psychiatry 46 (1999), pp. 1309-1320.

Baard, E.: The guilt-free soldier: New science raises the spectre of a world without regret. In: The Village Voice 22-28 January 2003.

Bale, T.L./Vale, W.W.: CRF and CRF receptors: Role in stress responsivity and other behaviours. In: Ann. Rev. Pharmacol. Toxicol. 44 (2004), pp. 525-57.

Ball, P.: Starting from scratch. In: Nature 431 (2004), pp. 624-626.

Boulanger, L.M./Shatz, C.J.: Immune signalling in neural development, synaptic plasticity and disease. In: Nature Reviews Neuroscience 5 (2004), pp. 521-531.

Bourgin, P. et al.: Hypocretin-1 modulates rapid eye movement sleep through activation of locus coeruleus neurons. In: J. Neurosci. 20 (2000), pp. 7760-67.

Bymaster F.P. et al.: Use of M1-M5 muscarinic receptor knockout mice as novel tools to delineate the physiological roles of the muscarinic choliergic system. In: Neurochem. Res. 28 (2003), pp. 437-442.

Carayannopoulos, L.N./Yokoyama, W.M.: Recognition of infected cells by natural killer cells. In: Current Opinion in Immunology 16 (2004), pp. 26-33.

CBW: “Non-Lethal” weapons, the CWC and the BWC, Editorial. In: The CBW Conventions Bulletin no. 61 (2003), p. 2.

Cello, J./Paul, A.V./Wimmer, E.:Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. In: Science 297 (2002), pp. 1016-1018.

Check, E.: Designs on life. In: Nature 438 (2005), pp. 417-418.

Check, E.: Harmful potential of viral vectors fuels doubts over gene therapy. In: Nature 423 (2003), pp. 573-574.

Church, G.: A Synthetic Biohazard Non-Proliferation Project 2004, available at: <http://arep.med.harvard.edu>.

Coghlan, M.J. et al.: Selective glucocorticoid receptor modulators. In: Annual Reports in Medicinal Chemistry 37 (2002), pp. 167-75.

Conahan, F.C.: Human Experimentation: An Overview on Cold War Era Programs, Testimony before the Legislative and National Security Subcommittee, Committee on Government Operations, House of Representatives, September 28th. GAO/T-NSIAD-94-266. Washington, D.C.: General Accounting Office 1994.

Craft, C.: Challenges of UNSCR 1540: Questions about International Export Controls. CITS Briefs. Athens: University of Georgia 2004.

Crone, H.: Banning Chemical Weapons. Cambridge: Cambridge University Press, 1992, pp.16-19.

Cronin, J. /Zhang, XY/Reiser, J: Altering the tropism of lentiviral vectors through pseudotyping. In: Current Gene Therapy, 5 (2005), pp. 387-398.

Dando, M.:The impact of the development of modern biology and medicine on the evolution of offensive biological warfare programs in the Twentieth Century. In: Defense Analysis 15 (1999), pp. 43-69.

Dando, M.R./Nathanson, V./Darvell, M.: Biotechnology, Weapons and Humanity. London: Harwood Academic Publishers 1999.

Dando, M.R./Rappert, B.: Codes of Conduct for the Life Sciences: Some Insights from UK Academia. Briefing Paper No. 16. Bradford: University of Bradford May 2005.

Dando, M.R./Wheelis, M.L.: Back to bioweapons? In: Bulletin of the Atomic Scientists 59 (2003) pp. 40-46.

Dando, M.R.: Chapter 6, The Human Nervous System. In: A New Form of Warfare: The Rise of Non-Lethal Weapons. London: Brassey's (1996).

Dando, M.R.: Chapter 8, An Assault on the Brain. In: A New Form of Warfare: The Rise of Non-Lethal Weapons. London: Brassey's 1996.

Dando, M.R.: Preventing Biological Warfare. The Failure of American Leadership. Basingstoke: Palgrave Macmillan 2002.

Dando, M.R.: Scientific and technological change and the future of the CWC: The problem of non-lethal weapons. In: Disarmament Forum 4 (2002) pp. 33-44.

Dando, M.R.: The Danger to the Chemical Weapons Convention from Incapacitating Chemicals. In: CWC Review Conference Paper No. 4, Department of Peace Studies, University of Bradford (2003) available at <http://www.brad.ac.uk/acad/scwc>.

Dando, M.R.: The New Biological Weapons: Threat, Proliferation and Control Boulder, CO: Lynne Rienner 2001, pp.103-116.

Datan, M.: Security Council Resolution 1540: WMD and non-state trafficking. In: Disarmament Diplomacy 79 (2005). pp. 48-60.

Davidov, E.J. et al.: Advancing drug discovery through systems biology. In: Drug Discovery Today 8 (2003), pp. 175-183.

Davis, S.S. Biomedical applications of nanotechnology-implications for drug targeting and gene therapy. In: Trends in Biotechnology 15 (1997), pp. 217-224.

Davis, S.S./Illum, L.: Absorption enhancers for nasal drug delivery. In: Clinical Pharmacokinetics 42 (2003), pp. 1107-1128.

de Lecea, L. et al.: The hypocretins: hypothalamus - specific peptides with neuroexcitatory activity. In: Proc. Nat. Acad. Sci. USA 95 (1998), pp. 322-27.

Docherty, J.R.: Subtypes of functional α_1- and α_2-adrenoceptors. In: European Journal of Pharmacology, 361 (1998), pp. 1-15.

Dubin, M.W.: How the Brain Works. Oxford: Blackwell 2002.

Dyk, D.-J./Lockley, S.W.: Functional genomics of sleep and circadian rhythm. In: J. Appl. Physiol. 92 (2002), pp. 852-862.

Edgewood RDEC: Scientific Conference in Chemical and Biological Defense Research: Abstract Digest. US Army Chemical and Biological Defense Command, Aberdeen Proving Ground, Maryland, 1989-94.

Editorial: New vistas for an old neurotransmitter. In: Biological Psychiatry 46 (1999), pp. 1121-1123. (Introduction to a special issue covering pages 1121-1320).

Esposito, P. et al.: Acute stress increases permeability of the blood - brain barrier through activation of brain mast cells. In: Brain Research 888 (2001), pp. 117-127.

Felder, C.C. et al.: Therapeutic opportunities for muscarinic receptors in the central nervous system. In: J. Medical Chemistry 43 (2000), pp. 4333-4353.

Fernandez-Pastor, B./Meana, J.J.: In vivo tonic modulation of the noradrenaline release in the rat cortex by locus coeruleus somatodendritic alpha2 adrenoceptors. In: European Journal of Pharmacology 442 (2002), pp. 225-229.
Ferrucci, L. et al.: Serum IL-6 level and the development of disability in older persons. In: J. Am. Geriatric Soc. 47 (1999), pp. 639-46.
Ferry B. et al.: Basolateral amygdala noradrenergic influences on memory storage are mediated by an interaction between β- and α_1-adrenoceptors. In: Journal of Neuroscience 19 (1999), pp. 5119-5123.
Ganter, B./Tugendreich, S./Pearson, C.I. et al.: Development of a large-scale chemogenomics database to improve drug candidate selection and to understand mechanisms of chemical toxicity and action. In: Journal of Biotechnology 119 (2005), pp. 219-244.
Garcia-Ojalvo, J. et al.: Modelling a synthetic multicellular clock: Repressilators coupled by quorum sensing. In: Proceedings of the National Academy of Sciences USA 101 (2004), pp.10955-60.
Geissler, E./Lohs, K.: The changing status of toxin weapons. In: Geissler, E. (ed.) Biological and Toxin Weapons Today. Oxford: Oxford University Press 1986, pp. 36-56.
Goldbeter, A.: Computational biology: a propagating wave of interest. In: Current Biology 14 (2004), pp. R601-R602.
Goldsby, R.A./Kindt, T.J./Osborne, B.A./Kuby, J.: In: Immunology, fifth edition. New York: W.H. Freeman and Company 2003.
Goodyear, C.S./Silverman, G. J.: Death by a B cell superantigen: in vivo V_H-targeted apoptotic supraclonal B cell deletion by a staphylococcal toxin. In: Journal of Experimental Medicine 197 (2003), pp. 1125-1139.
Gordon, J./Barnes, N.N.: Lymphocytes transport serotonin and dopamine: agony or ecstasy? In: Trends in Immunology 24 (2003), pp. 438-443.
Graff, C.L./Pollack, G.M.: Nasal drug administration: potential for targeted central nervous system delivery. In: Journal of Pharmaceutical Sciences 94 (2005), pp. 1187-1195.
Gupta, S./Ferguson, N./Anderson, R.: Chaos, persistence, and evolution of strain structure in antigenically diverse infectious agents. In: Science 280 (1998), pp. 912-915.
Hamerman, D.: Toward an understanding of frailty. In: Annals of Internal Medicine 130 (1999), pp. 945-50.
Harris, E.D./Steinbruner, J.D.: Scientific openness and national security. In: Chemical and Biological Weapons Conventions Bulletin 67 (2005), pp. 1-6.
Harvard Mental Health Letter: The mind and the immune system. April 2002. Available at <http://www.health.harvard.edu/medline/mental/M0402a.html>.
Hasenclever, A./Mayer, P./Rittberger, V.: Fair Burden-Sharing and the Robustness of International Regimes: The Case of Food Aid. In: Tübinger Arbeitspapiere zur Internationalen Politik und Friedensforschung Nr.31. Tübingen (1998), p.1.
Hasenclever, A./Mayer, P./Rittberger, V.: Theories of International Regimes. Cambridge: Cambridge University Press 1997.
Haystead, J.: New particle engineering technology improves drug solubility, In: Pharmaceutical Technology 27 (2003), pp. 18-19 and 114.
Henry, C.M.: Systems biology: Integrative approach to drug discovery. In: Chemical and Engineering News 19 May (2003), pp. 45-55.
Ideker, T./Galitski, T./Hood, L.: A new approach to decoding life: Systems biology. In: Ann. Rev. Genomics Hum. Genet. 2 (2001), pp. 343-372.
Inui, A.: Cytokines and sickness behaviour: implications from knockout models. In: Trends in Immunology 22 (2001), pp. 469-473.

Jackson, R. J./Ramsay, A. J./Christensen, C./Beaton, S./Hall, D. F. R./Ramshaw, I. A.: Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. In: Journal of Virology 75 (2001), pp. 1205-1210.

Kaneta, T./Kusnecov, A.W.: The role of central corticotropin-releasing hormone in the anorexic and endocrine effects of the bacterial T cell superantigen, Staphylococcal enterotoxin A. In: Brain, Behaviour, and Immunity 19 (2005), pp. 138-146.

Kaplan, D.E./Marshall, A: The Cult at the End of the World, London: Hutchinson, 1996.

Karwa, M. et al.: Bioterrorism: Preparing for the impossible or the improbable. In: Critical Care Medicine 33 (2005), pp.575-595.

Kelle, A.: Bioterrorism and the Securitization of Public Health in the United States of America – Implications for Public Health and Biological Weapons Arms Control. Bradford Regime Review Paper No. 2. Bradford: University of Bradford July 2005, available at: <http://www.brad.ac.uk/acad/sbtwc/regrev/Kelle_SecuritizationinUS.pdf>.

Kelle, A.: The CWC after its first review conference: is the glass half full or half empty? In: Disarmament Diplomacy 71 (2003), pp. 31-40.

Ketchum, J.S./Sidell, F.R.: Incapacitating Agents. In: Sidell, F.R./Takafuji, E.T./Franz, D.R. (eds), Medical Aspects of Chemical and Biological Warfare. Washington, DC: Office of the Surgeon General 1997, pp.287-306.

Kiecolt-Glaser, J.K. et al.: Psychoneuroimmunology: psychological influences on immune function and health. In: Journal of Consulting and Clinical Psychology 70 (2002), pp. 537-47.

Kitano, H.: Systems biology: A brief overview', Introduction to a special section on systems biology: the genome, ligome and beyond. In: Science 295 (2002), pp. 1662-1664.

Knickerbocker, B.: Military looks to drugs for battle readiness: As combat flights get longer, pilot use of amphetamines grows, as do side effects. In: The Christian Science Monitor (9 August 2002).

Kraljevic, S./Stambrook, P.J./Pavelic, K.: Accelerating drug discovery. EMBO reports 5 (2004), pp. 837-842.

Kubera, M./Maes, M.: Serotonin-immune interactions in major depression. In: Patterson, P./Kordon, C./Christen, Y. (eds.), Neuro-Immune Interactions in Neurologic and Psychiatric Disorders. Berlin: Springer 2000, pp. 79-87.

Lachowicz, J.E. et al.: Discovery of SCH211803, a high affinity, selective M2 receptor antagonist and a novel approach to treatment of Alzheimer's disease. In: Soc. Neurosci. Abstr. 27 (2001), p. 679.

Lakoski, J.M. et al.: The Advantages and Limitations of Calmatives for Use as a Non-Lethal Technique. Applied Research Laboratory, College of Medicine, Pennsylvania State University, 2000.

Lehrman, T.D.: Rethinking interdiction: the future of the proliferation security intitiative. In: The Nonproliferation Review 11 (2004), pp.1-45.

Leitenberg, M.: The Experience of the Japanese Aum Shinrikyo Group and Biological Agents, In: B. Roberts (ed.), Hype or Reality: The ”New Terrorism” and Mass Casualty Attacks. Alexandria, VA: CBACI, 2000, pp.159-170.

Levy, M.A. et al.: The study of international regimes. In: European Journal of International Relations 1 (1995), pp. 267-330.

Licinio, J./Frost, P.: The neuroimmune-endocrine axis: pathophysiological implications for the central nervous system cytokines and hypothalamus-pituitary-adrenal hormone dynamics. In: Brazilian Journal of Medical and Biological Research 33 (2000), pp. 1141-1148.

Longstaff, A.: Instant Notes: Neuroscience, 2nd Edition. New York: Taylor and Francis 2005.

Lundberg, C./Jungles, S.J./Mulligan, R.C.: Direct delivery of leptin to the hypothalamus using recombinant adeno-associated virus vectors results in increased therapeutic efficacy. In: Nature Biotechnology 19 (2001), pp. 169-172.

McGough, J.L. et al: Amygdala modulation of memory consolidation: Interaction with other brain systems. In: Neurobiology of Learning and Memory 78 (2002), pp. 539-552.

Medzhitov, R./Preston-Hurlburt, P./Janeway, C.A., Jr.: A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. In: Nature 388 (1997), pp. 394-397.

Minton, K.: Immune evasion. Germ warfare. In: Nature Reviews Immunology 3 (2003), pp. 442-443.

Moon, J.E.v. C.: Chapter 2. The US BW Program: dilemmas of policy and preparedness. In: Wheelis, M./Rozsa, L./Dando,M.R. (eds.): Deadly Cultures: Bioweapons from 1945 to the Present. Cambridge: Harvard University Press 2006.

Mourez, M./Kane, R.S./Mogridge, J./Metallo, S./Deschatelets, P./Sellman, B.R./Whitesides, G.M./Collier, R.J.: Designing a polyvalent inhibitor of anthrax toxin. In: Nature Biotechnology 19 (2001), pp. 958-961.

Müller, H. et al.: Regime unter Stress. Beharrungs- und Anpassungsleistungen internationaler Regime unter den Bedingungen existenzgefährdender Herausforderungen. Frankfurt/Main: PRIF, February 1999, unpublished manuscript.

NAS: National Academies of Science: National Research Council of the National Academies Committee on Research Standards and Practices to Prevent the Destructive Application of Biology. In: Biotechnology Research in an Age of Terrorism. Washington, DC: The National Academies Press (2004).

National Institutes of Health: Gene more than doubles risk of depression following life stresses. In: NIH News Release (17 July 2003), available at <www.nimh.nih.gov/events/prgenestress.cfm>.

National Institutes of Health: NAID biodefence research agenda for CDC category A agents. Progress Report, August 2003. <http://www.niaid.nih.gov/biodefense/research/bioresearchagenda.pdf>.

National Institutes of Health: Stress system malfunction could lead to serious, life threatening disease. In: NIH Backgrounder (9 September 2002), available at <http://www.nih.gov/news/pr/sep2002/nichd-09.htm>.

NSABB website at <www.biosecurityboard.gov/>.

OPCW, Note by the Director-General. Report of the Scientific Advisory Board on Developments in Science and Technology, document RC-1/DG.2. The Hague: United Nations, 23 April 2003, p. 15.

Pacheco-Lopez, G. et al.: Behavioural endocrine immune-conditioned response is induced by taste and superantigen pairing. In: Neuroscience 129 (2004), pp. 555-562.

Pearson, G.S.: Prospects for chemical and biological arms control: The web of deterrence. In: The Washington Quarterly 16 (1993), pp. 145-162.

Pearson, G.S.: Report from Geneva No. 23: The Biological Weapons Convention Meeting of Experts. In: The Chemical and Biological Weapons Conventions Bulletin 68 (2005), pp.12-19.

Pearson, G.S.: Security and oversight of pathogenic microorganisms and toxins. In: Chemical and Biological Weapons Conventions Bulletin 60 (2003), pp. 6-15.

Petty, M.A./Lo, E.H.: Junctional complexes of the blood-brain barrier: permeability changes in neuroinflammation. In: Progress in Neurobiology 68 (2002), pp. 311-323.

Poltorak, A./He, X./Smirnova, I./Liu, M.Y./Huffel, C.V./Du, X./Birdwell, D./Alejos, E./Silva, M./Galanos, C. et al.: 1998 Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in *Tlr4* gene. In: Science 282 (1998), pp. 2085-2088.

Poste, G.: Advances in biotechnology: promise or peril. Available at: < www.hopkins-defense.org/sympcast/transcripts.trans_poste.html>.

Prakosh, K.M./Lo, Y.L.: The role of clinical neurophysiology in bioterrorism. In: Acta Neurol. Scand. 111 (2005), pp. 1-6.

Rietschel, E.T./Brade, H.: Bacterial endotoxins. In: Scientific American 267 (1992), pp. 54-61.

Robinson, J.P.:1998, The Negotiations on the Chemical Weapons Convention: a historical overview. In: Bothe,M./Ronzitti, N./Rosas, A. (eds.): The New Chemical Weapons Convention-Implementation and Prospects. The Hague: Kluwer Law International 1998, pp. 17-36.

Rojas I.G. et al.: Stress-induced susceptibility to bacterial infection during cutaneous wound healing. In: Brain, Behaviour and Immunity 16 (2002), pp. 74-84.

Roozendaal, B.: Glucocortcoids and the regulation of memory consolidation. In: Psychoneuroendocrinology 25 (2000), pp. 213-218.

Rosengard, A. M./Liu, Y./Nie, Z./Jimenez, R.: Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement. In: Proceedings of the National Academy of Sciences USA 99 (2002), pp. 8808-8813.

Royal Society: Royal Society Submission to the Foreign and Commonwealth Office Green Paper on Strengthening the Biological and Toxin Weapons Convention. Policy Document 25/02. London: Royal Society 2002.

Sahoo, S.K./ Labhasetwar, V.: Nanotech approaches to drug delivery and imaging. In: Drug Discovery Today 8 (2003), pp. 1112-20.

Sakurai, T. et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behaviour. In: Cell 92 (1998), pp. 573-85.

Sandy, P./Ventura, A./Jacks, T.: Mammalian RNAi: a practical guide. In: BioTechniques 39 (2005), pp.215-224.

Shohet, S./Wood, G.: Delivering biotherapeutics-technical opportunities and strategic trends. In: Journal of Commercial Biotechnology 9 (2002), pp. 59-66.

Sidell, F.R.: Nerve Agents. In: Sidell, F.R./Takafuji, E.T./Franz, D.R. (eds), Medical Aspects of Chemical and Biological Warfare. Washington, D.C.: Office of the Surgeon General, US Army 1997, pp.129-180.

Silverman, G.J. et al.: The dual phases of the response to a neonatal exposure to a V_H family-restricted staphylococcal B cell superantigen. In: Journal of Immunology 161(1998), pp. 5720-5732

Sims, N.A.: Remedies for the Institutional Deficit of the BTWC: Proposals for the Sixth Review Conference. Review Conference Paper No.12. Bradford: University of Bradford March 2005. Available at <http://www.brad.ac.uk/acad/sbtwc>.

SIPRI: The Problem of Chemical and Biological Warfare. Volume I: The Rise of CB Weapons. Stockholm: Almqvist and Wiksell 1971, pp. 26-58.

SIPRI: The Problem of Chemical and Biological Warfare, Volume II of CB Weapons Today. Stockholm: Almqvist and Wiksell 1973, pp. 288-308.

Small, K.M. et al.: Pharmacology and physiology of human adrenergic receptor polymorphisms. In: Annu. Rev. Pharmacol. Toxicol. 43 (2003), pp. 381-411.

Southwick, S.M. et al.: Role of norepinephrine in the pathophysiology and treatment of post-traumatic stress disorder. In: Biological Psychiatry 46 (1999), pp. 1192-1204.

Spence, S.: Achieving Effective Action on Universality and National Implementation: the CWC Experience. Briefing Paper No. 13. Bradford: University of Bradford April 2005.

Steinbruner, J.D./Harris, E.D.: Controlling dangerous pathogens. In: Issues in Science and Technology 19 (2003). Available at <http://www.issues.org/issues/19.3/steinbruner.htm>.

Steinman, L.: Elaborate interactions between the immune and nervous systems. In: Nature Immunology 5 (2004), pp. 575-581.

Sternberg, E.M.: SNIB: Section on Neuroendocrine Immunology and Behavior 2003, available at <http://intramural.nimh.nih.gov/snib/>.

Sternberg, E.M.: The stress response and the regulation of inflammatory disease. In: Annals of Internal Medicine 117 (1992), pp. 854-66.

Straub, R.H./Westermann, J./Schölmerich, J./Falk, W.: Dialog between the CNS and the immune system in lymphoid organs. In: Immunology Today 19 (1998), pp. 409-413.

Sunshine Project, documentation of the US non-lethal weapons programmes, at <www.sunshine-project.org>.

Taheri, S. et al.: The role of hypocretins (orexins) in sleep regulation and narcolepsy. In: Annu. Rev. Neurosci. 25 (2002), pp. 283-313.

Thomas, C.E./Ehrhardt, A./Kay, M.A.: Progress and problems with the use of viral vectors for gene therapy. In: Nature Reviews Genetics 4 (2003), pp. 346-358.

Tortorella, D. et al.: Viral subversion of the immune system. In: Annual Review of Immunology 18 (2000), pp. 861-926.

Tsai, S.M. et al.: Pyrogens enhance β-endorphin release in hypothalamus and trigger fever that can be attenuated by buprenorphine. In: Journal of Pharmacological Science 93 (2003), pp. 155-162.

Tucker, J.B.: Biosecurity: Limiting Terrorist Access to Deadly Pathogens. In: Peaceworks No.52. Washington, DC: United States Institute of Peace (November 2003), pp. 1-52.

Ulrich, R.G. et al.: Staphylococcal enterotoxin B and related pyrogenic toxins. In: Sidell, F.R. et al. (eds), Medical Aspects of Chemical and Biological Warfare. Washington DC: Office of the Surgeon General, US Army 1997, pp.621-630.

United Nations: Background Paper: New Scientific and Technical Developments Relevant to The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. Document BWC/CONF.III/4. Geneva: United Nations, 26 August 1991. Available at <http://www.opbw.org>.

United Nations: Background Paper: New Scientific and Technical Developments Relevant to The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. Document BWC/CONF.V/4. Geneva: United Nations 14 September 2001. Available at <http://www.opbw.org>.

United Nations: Background Paper: New Scientific and Technical Developments Relevant to The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. Document BWC/CONF.4/Add.1. Geneva: United Nations 26 October 2001. Available at <http://www.opbw.org>.

United Nations: Depository States: New Scientific and Technical Developments Relevant to The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. Document BWC/CONF.I/5. Geneva: United Nations, 6 February 1980. Available at <http://www.opbw.org>.

United Nations: Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction: Report of the Meeting of States Parties. Document BWC/MSP/2003/4 (Vol. I). Geneva: United Nations 26 November 2003. Available at <http://www.opbw.org>.

United Nations: Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction: Report of the Meeting of States Parties. Document BWC/MSP/2004/3. Geneva: United Nations 14 December 2004. Available at <http://www.opbw.org>.

United Nations: Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction: Report of the Meeting of States Parties. Document BWC/MSP/2005/MX/3. Geneva: United Nations 5 August 2005. Available at <http://www.opbw.org>.

United Nations: United Nations Security Council Resolution 1540. Adopted by the Security Council at its 4956th Meeting, on 28 April 2004, available at <http://disarmament2.un.org/Committee1540/Res1540(E).pdf >.

United States, Secretary of Health and Human Services: Charter. National Science and Advisory Board for Biosecurity. Washington, DC 2004, dated 4 March, available at <www.biosecurityboard.gov/SIGNED%20NSABB%20Charter.pdf>.

US Army Intelligence Agency: Letter Report: Incapacitating Agents, European Communist Countries, AST-1620R-100-90, US Army Foreign Science and Technology Center, 16 July 1990.

US Department of State, Bureau of Public Affairs: Proliferation Security Initiative. Washington, DC: 15 September 2003. Available at <http://www.state.gov/documents/organization/24252.pdf>.

USAMRIID: Basic studies seeking generic medical countermeasures against agents of biological origin. In: Annual Report for Fiscal Year 1987, p. 19.

Van Gelder, R.N. et al.: Circadian rhythms: In the loop at last. In: Science 300 (2003), pp.152-153.

Vermetten, E./Bremner, J.D.: Circuits and systems in stress: I. Preclinical studies. In: Depression and Anxiety 15 (2002), pp. 126-147.

Vogt, G.: Multi-axis robots bring automation to life sciences. In: Industrial Robot: An International Journal 29 (2002), pp. 49-52.

Wang, G.K./Sehgal, A.: Signalling components that drive circadian rhythms. In: Current Opinion in Neurobiology 12 (2002), pp. 331-338.

Ward, K.D.: The BWC Protocol: Mandate for Failure. In: The Nonproliferation Review 11 (2004), pp.183-99.

Wax, P.E./Becker, C.E./Curry, S.C.: Unexpected “gas” casualties in Moscow: a medical toxicology perspective. In: Annals of Emergency Medicine 41 (2003), pp. 700-705.

Webster, J.I./Tonelli, L./Sternberg, E.M.: Neuroendocrine regulation of immunity. In: Annu. Rev. Immunol. 20 (2002), pp. 125-63.

Wheelis, M.: Biotechnology and biochemical weapons. In: The Nonproliferation Review 9 (2002), pp. 48-53.

Whittaker, P.A.: What is the relevance of bioinformatics to pharmacology? In: Trends in Pharmacological Sciences 24 (2003), pp. 34-39.

Wood, A./Scott, A.: Combinatorial chemistry picks up speed. In: Chemical Week 162 (9 August 2000), pp. 39-42.

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Arbeitspapiere DSF:

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- Die Rolle von Religionen in Gewaltkonflikten und Friedensprozessen. Osnabrück 2007 (Heft 2).
- Grundprobleme der Konfliktbeteiligung und Friedenkonsolidierung mit besonderer Berücksichtigung der Konfliktherde auf dem afrikanischen Kontinent. Osnabrück 2007 (Heft 3).